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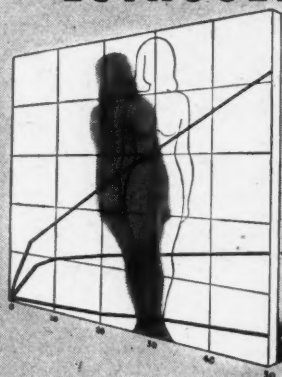
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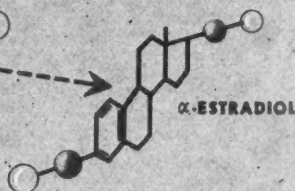
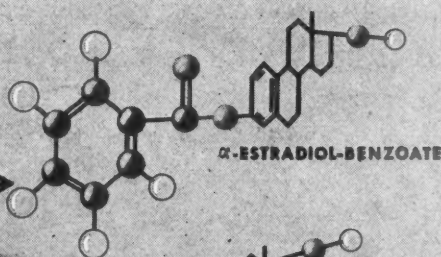
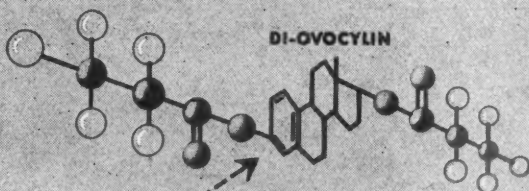
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# American Journal of Obstetrics and Gynecology

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## Original Communications

### CARCINOMA OF THE CERVIX AND PREGNANCY\*

#### A Clinical Study of Eight Cases

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CARCINOMA of the cervix occurring during pregnancy is a tragic complication. In the past five years, we have observed eight such cases on the obstetric services of Cook County Hospital. These patients were distributed as follows: The first one was seen in 1939, the second in 1941, and the last six in 1943. This unusual increase in the last year has impressed the entire personnel of our department that this is a complication for which we must always be on the alert.

#### Etiology and Pathogenesis

During pregnancy, one rarely observes carcinoma of the cervix. Carcinoma appears in appreciable numbers in an age group when the child-birth incidence has decreased decidedly. In our series of patients, the youngest was 25 and the oldest 43 years of age. All except the youngest were older than the average age of the rest of our obstetric patients.

Due to the uneven distribution of our series, whereby three-quarters of our cases appeared in one year, we did not attempt to establish a percentage incidence at Cook County Hospital. Danforth,<sup>1</sup> in an analysis of accumulated figures, finds the frequency to be about 0.032 per cent. Baer<sup>2</sup> states that one in 10,000 pregnancies represents the general average with an explanation for its infrequency to be found in the alterations in the cervix by the carcinoma so that "Fertilization may thus be prevented mechanically, chemically or because coitus becomes impossible or repulsive."

\*Presented at a meeting of the Chicago Gynecological Society, February 18, 1944.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."



It is well known that most of the patients exhibiting carcinoma of the cervix are multipara. Parturition and abortions are the most frequent causes of lacerations, infection and erosion of the cervix. These changes are believed by many to make a favorable background for the development of cancer of the cervix at a later date. In this series, the ratio of multipara to primipara was three to one, whereas in all the rest of our pregnant patients, it is only about five to three. In a study of many other reports, we noted that the occurrence of cervical carcinoma was even much less frequent in women having their first pregnancy. Hofbauer,<sup>3</sup> in a histologic study of apparently normal cervixes during pregnancy, found epithelial proliferation which was similar to premalignant phenomena seen in other organs, and which is regarded by him to be a factor in the possible production of malignancy at a later date. Perhaps a deflection of these proliferative changes in the cervical epithelium may be a precipitating factor of malignant development during pregnancy, since the whole endocrine mechanism is then profoundly altered.

While no race is immune to carcinoma of the cervix, an interesting observation in our small series indicated that this malignant growth might be more prone to occur during pregnancy in the white race. White patients outnumbered Negroes by 5 to 3, whereas in the same period of time, a tabulation of all the rest of our patients indicated that Negroes were in excess in proportions of about 2 to 1.

### Pathology

The altered physiology of the cervix during a pregnancy must considerably influence a malignancy originating therein. It is believed by many that the carcinoma precedes the pregnancy, and is only a small growth at the time of conception. The malignancy is usually a squamous cell growth, but may in about ten per cent of cases originate from the glandular portion of the cervix.

The histologic pathology of the tumors, in all cases except one, was studied from the biopsy. While small tissue specimens serve their purpose well in establishing the diagnosis, one may be frequently led astray in using them for speculating upon the malignancy potential. For this reason, we made no attempt to grade the tumors pathologically.

Our material was studied with hematoxylin and eosin stains, and most of them had evidences that the tumor tissue grows in a very vascular field as indicated by numerous dilated blood vessels (Fig. 1). The connective tissue stroma is small in amount, and numerous mitotic figures are seen. In some specimens many polymorphonuclear and lymphocytic cells were seen around the clusters of malignant cells. One of our biopsy specimens showed that the neoplasm was extending into the adjacent anterior vaginal squamous cell epithelium (Fig. 2). An adenocarcinoma was noted only once in our series. This was the patient that lived only three hours after admission and at autopsy the chief findings were an ulcerated intrinsic carcinoma of the cervix infiltrating the surrounding pelvis and urinary bladder, and with small metastases to the periaortic lymph nodes. The mucosa was entirely missing and replaced by a necrotic granular membrane. Beneath the membrane and extending throughout the entire wall were numerous dark-staining irregular glands. Between the latter there was more connective tissue than noted in our other cases. In places, the dark-staining cells lost their glandular arrangement and were replaced by solid cords. When the patients carried their pregnancies into the last trimester the neoplasms attained

large proportions, and most frequently (5 out of 7) were of the evertans type of growth as a vascular cauliflower-like tumor. A study of our tissue specimens as a group gave us the impression that there was a definite trend to anaplasia with a loss of polarity of the cells rather than a maturity in the histologic pathology (Fig. 3).

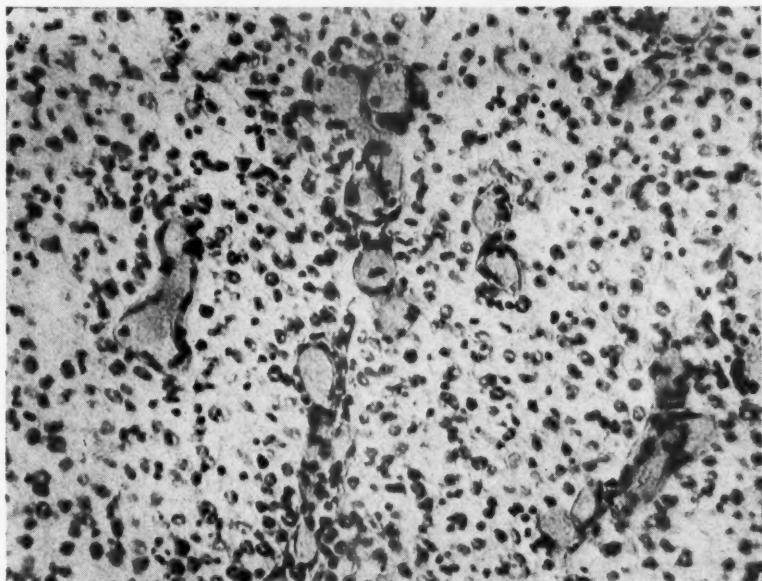


Fig. 1.—Numerous dilated blood vessels demonstrating the vascularity of the carcinoma (Case 5).  $\times 126$ .

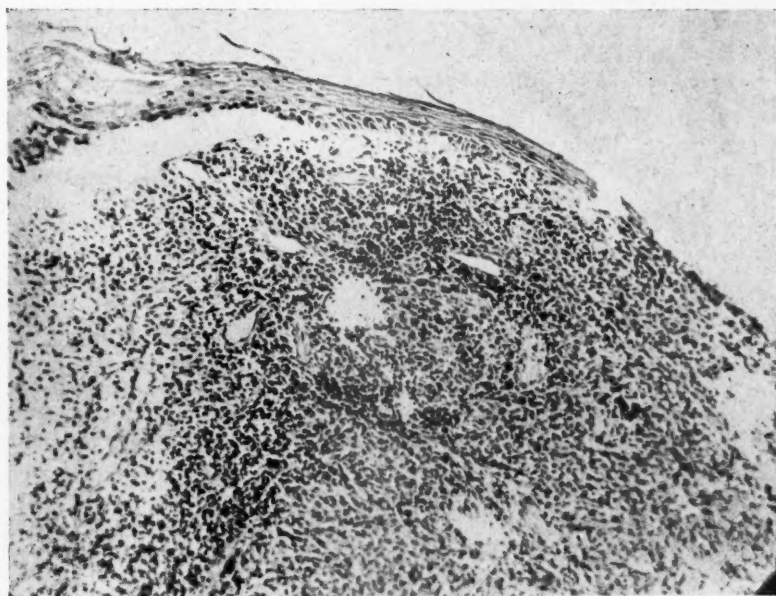


Fig. 2.—Carcinoma cells growing close to the vaginal mucosa anterior to the cervix (Case 1).  $\times 33$ .

### Case Histories

The clinical features of cancer of the cervix during pregnancy, as noted in our series, may be brought out in a brief résumé of their case histories. They are presented in accordance to the period of gestation that the diagnosis was established, because the problem and its management thus differs.

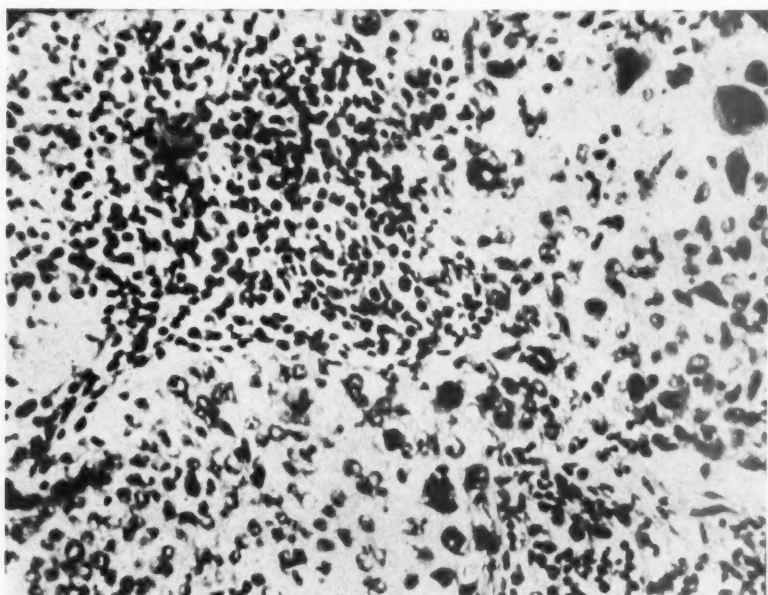


Fig. 3.—Anaplastic character of the carcinoma (Case 4). The cells are seen varying in size and shape, there is also a hyperchromasia, mitotic figure (below center) and a giant cell (upper right corner).  $\times 300$ .

### Carcinoma During Early Pregnancy

CASE 1.—C. H., white, 35 years of age, gravida vi, para v, began prenatal care when she was about ten weeks pregnant. Her last menstrual period was 7/17/43, and in her second month, she bled a moderate amount which lasted for about one hour. This was a spontaneous bleeding with no relationship to any preceding event. A routine vaginal examination revealed that there was a hard nodular growth on the anterior lip of the cervix about 1.5 by 2 centimeters. This growth was closer to the anterior vaginal wall, and where the latter joined the cervix, there was a narrow, transversely directed superficial ulceration that bled moderately following the examination. There were no parametrial changes. A biopsy from the nodular portion of the cervix and the adjacent reflecting anterior vaginal mucosa revealed an infiltrating nonhornifying squamous cell carcinoma involving the cervix and the adjacent vaginal wall. She was referred to the department of radiotherapy, where in four weeks, she received 19 deep x-ray treatments for a total dosage of 2,850 r.\* to the cervix through 4 external fields. The uterus then appeared smaller, the Friedman test was negative, and the patient was sent in for radium therapy. On 12/8/43, 1,500 mg. hours of radium were given. The next day, she developed abdominal pains and

\*The r. dosage referred to above, or hereafter, will indicate the number of r. units delivered to the cervix itself as computed by depth dose charts.



24 hours thereafter, she extruded a macerated fetus which was evidently dead for a long time. The placenta delivered 24 hours after the extrusion of the fetus. Examination now showed that the nodule in the anterior cervical lip had definitely decreased in size, the small area of ulceration anterior to it had healed, and the parametria were not indurated. Four weeks later, she received two more radium treatments to make a total of 4,500 mg. hours. She is still under observation receiving deep x-ray therapy. Barring unforeseen complications, her prognosis at this time appears to be favorable.

### Carcinoma During Late Pregnancy

CASE 2.—L. G., Negro, aged 33 years, gravida i, last menstruated 8/6/38. Prenatal care began in her third month and routine vaginal examination failed to reveal anything significant. Wassermann test was positive and she received antiluetic treatment. She had a moderate blood pressure elevation on 2/21/39, and was admitted on 4/11/39 with complaints of headaches, a trace of albumin, and a blood pressure elevation which ranged from 140 to 160 systolic, and a diastolic level of 90 to 110 mm. Hg. The patient had no edema, and her fetus appeared smaller in size than the period of gestation would indicate. Four days later, the fetal heart tones could not be heard. A medical induction was tried and twice failed. A bag induction because of persistent blood pressure elevation and a retinal hemorrhage was attempted (4/17/39). The cervix was felt to be definitely abnormal. The anterior lip was soft, irregularly polypoid and friable. The posterior lip, which was indurated, felt like a band that was parallel with the external os. Pieces of the friable tissue broke off and were sent to the laboratory for examination. The bag of waters ruptured during this examination, and a pulseless cord that prolapsed was cut off. The pathology report of the tissue was "nonhornifying squamous cell carcinoma of the cervix." The patient's temperature rose to 102.4° F., and the pulse 140 per minute. The discharged amniotic fluid became purulent and had a very offensive odor. On 4/20/39, the fetus and uterus were removed together as one would remove a huge fibroid. The supracervical portion of the uterus was amputated between clamps to avoid spill of infectious substance. The patient had a stormy postoperative course. The incision became superficially infected and broke down. A puerperal pyelitis developed on the tenth day postoperative. In six weeks she was getting deep x-ray therapy followed by two treatments of radium totaling 3,000 mg. hours. In a period of 17 months, she received 69 roentgen treatments for a total dosage of 17,275 r. of which 9,100 r. was through an intravaginal cone and 8,175 r. through 6 external portals. When seen one year later, she had no trace of the original tumor. Two years later, she had a bowel obstruction that cleared up without any operation. She never returned thereafter. We were informed that she left Chicago three years after the operation in poor health to return to her home in the South. It is our opinion that she had a recurrence, and probably died shortly after leaving the city.

CASE 3.—L. W., Negro, aged 31, para iv, gravida vii, last menstruated 5/20/40. Prenatal care began in the third month, but no significant findings were noted concerning the cervix. She spotted blood frequently during pregnancy and in her sixth month (11/26/40), she was admitted to the hospital for a suspected placenta previa. The obstetrical resident recorded that the cervix was large and purplish in color, and

that "a large erosion on the anterior lip" bled rather profusely on contact. This was readily controlled by a silver nitrate stick application, and she was discharged two days later. She was again admitted on 1/18/41, as a multipara in labor. She bled rather profusely shortly after this admission, and vaginal examination revealed a large, fungating, punched out, red, raw area, 3 by 4 cm., on a very large hypertrophied anterior cervical lip. This was dark blue and was so indurated, that it had a cartilaginous feel. The parametria were not infiltrated. A biopsy of this suspicious area revealed "an infiltrating nonhornifying squamous cell carcinoma." On 1/24/41, a Porro cesarean section and bilateral salpingo-oophorectomy were performed. Postoperative recovery was good and the patient was discharged on the thirteenth day, with instructions to return to the Gynecology Tumor Clinic, where patients for pelvic radium therapy are managed. This patient did not go to the tumor clinic as instructed, but went to the Outpatient Radiotherapy Clinic, where in a period of four and one-half months she received 65 x-ray treatments through six fields for a 10,000 r. dosage, but never any radium treatment. Despite regular x-ray treatments, which began shortly after her discharge from the obstetrical department, she had a progressively downhill course. On 9/24/41, she reappeared in the gynecology department because of considerable vaginal and rectal bleeding. A tumor mass filled the entire pelvis. She was given palliative treatment, but continued to bleed intermittently. She died ten months after her delivery, but no postmortem examination was permitted.

CASE 4.—B. F., Negro, aged 32, para i, gravida ii, last menstruated on 5/25/42. Her first prenatal examination was in her sixth to seventh month at another clinic, where a certified obstetrician who examined her noted that the cervix was badly eroded and lacerated, and bled freely. Nevertheless, he failed to regard this as significant and on 2/28/43, she passed several blood clots and noted that when she urinated, she would bleed profusely. One hour later, she was admitted to the obstetric service and a tentative diagnosis of placenta previa was considered. Vaginal examination revealed a posterior cervical lip replaced by a large cauliflower-like mass about 7 by 4 centimeters. The mass had a broad base, was irregular and the surface bled on the least contact by gauze or cotton. The left parametrial zone definitely felt infiltrated. A biopsy revealed an anaplastic nonhornifying squamous cell carcinoma of the cervix. The tumor mass bled off and on. A classical cesarean section was performed on 3/2/43, at 7:00 P.M. Her temperature was 100.4° F., and pulse 96 per minute in the afternoon. From the operative field, the mass could be seen extending up the cervix. It was bleeding and was only controlled by a pressure pack that was inserted vaginally. For the next three days, the temperature ranged up to 101° F. The abdomen was markedly distended and the pulse spiked to 120 and 140. The highest temperature elevation was 102.2° F. on the sixth day, and gradually declined. During this period, she had received two blood transfusions and sulfathiazole. On the eighth day, a catheterized specimen of urine showed pus cells in clumps, but after the tenth day, the temperature remained normal. On 3/26/43, she was discharged and referred to the tumor clinic. The baby had died within 24 hours from an aspiration pneumonia. X-ray treatments for the mother were started three days before discharge. She had only 14 radiation treatments, and she did not attend the tumor clinic as advised, and never returned in spite of all efforts to contact her.

CASE 5.—B. B., white, aged 38, gravida xv, para x, last menstruated 6/24/42. She had no prenatal care and was admitted to the hospital when she was about five and one-half months pregnant for a possible threatened abortion. The bleeding promptly stopped with bed rest and she left the hospital six days later, but never reported to the prenatal clinic as instructed. She continued to bleed off and on which would necessitate bed for relief. On 2/28/43, she passed large blood clots and four days later presented herself at the hospital for readmission. She was now eight and one-half months pregnant. Upon vaginal examination, with precautions observed when a placenta previa is suspected, we found a markedly lacerated cervix and the anterior lip was chiefly involved in a markedly but irregularly hypertrophied, almost cauliflower-appearing tumor mass. It was very vascular, bled freely on touch, and had a firm cartilaginous feel. The entire cervix was almost four times the normal size. Some of the epithelium of the anterior lip was grayish in appearance resembling a surface necrosis. Biopsy of this mass revealed a nonhornifying squamous cell carcinoma. A classical cesarean section was performed on the second day in the hospital. The postoperative course was entirely uneventful. On the thirtieth postoperative day, the red count was 2.45 and the hemoglobin was 44 per cent. The only temperature elevation was 100° F. on the fourth day postoperative. She was given a transfusion of 500 c.c. of blood on the fifth postoperative day. X-ray therapy was started the sixth postoperative day, and she was discharged from the hospital on the sixteenth day with instructions to return for a continuation of radiation therapy. She was readmitted in two months after her discharge to the gynecology ward, and the tumor mass, despite thirty-four treatments of radiation, had become very far advanced, and the pelvis was "frozen" so no radium therapy was used. The patient continued to receive deep x-ray therapy for a total of 60 treatments through 6 external portals for a total dosage of 9,000 r. She was last seen again in the gynecology ward on 12/1/43, in a terminal condition.

CASE 6.—A. V., white, gravida iv, para iii, was under the care of a private doctor. She was admitted to the obstetric ward on 7/29/43, when she was apparently almost full term. She had no pains, but came to the hospital because she had slight bleeding at 7:30 that morning. Her membranes ruptured at 10:30 A.M. and mild pains were noted. The bleeding was interpreted by the resident staff to be a possible bloody show. A vaginal examination revealed a cauliflower mass that was hard, friable and bled with the least manipulation. A biopsy revealed a nonhornifying squamous cell carcinoma. On the evening of admission, a classical cesarean section was performed under local anesthesia. The postoperative course was entirely uneventful. The highest temperature was 100.2° F. on the seventh day. X-ray therapy was started on the sixth day, and she received 3 irradiations when discharged on the fifteenth postoperative day. She was given 60 radiation treatments between 8/4/43, and 11/27/43, through 6 fields for a total dosage of 7,000 r. The tumor clinic following the course of this patient examined her eight weeks after her operation, and found the entire posterior cervical lip was replaced by a craterlike ulcer which was continuous with an induration posteriorly in the direction of the rectovaginal septum. The parametria were fixed. With these findings, radium treatment was deemed to be unwise since a rectovaginal fistula was very likely to occur. The only treatment available would be palliation by further use of deep x-ray therapy.



CASE 7.—M. S., white, gravida vi, para vii, aged 43, had no prenatal care. She was admitted to the obstetric service on 9/3/43, with a history of bleeding for the past four weeks. During the week prior to her admission, the bleeding had become very marked, and she did not feel life after that time. On the day of admission, she had cramplike pains that were not typical of labor pains. Her condition was very poor. She was in profound shock; her blood pressure was 50 systolic and 35 diastolic. Although she received 500 c.c. of plasma, 1,000 c.c. of blood and 1,000 c.c. of saline, she did not rally. A vaginal examination revealed that the entire cervix was very hard and markedly eroded, and was covered by a shaggy, gray, friable tissue over the whole of its canal. The structures adjacent to the cervix were infiltrated with especial involvement of the posterior wall of the bladder. The patient expired three hours after admission. At autopsy, the essential anatomic findings were: 1. Ulcerated intrinsic carcinoma of the cervix with infiltration into the surrounding pelvis and urinary bladder. 2. Intact seven-month pregnancy with a macerated fetus presenting a breech at the inlet. 3. Small metastasis to the left periaortic lymph nodes. The histopathologic findings of cervix revealed an adenocarcinoma with areas where the cells lost their glandular arrangement and formed solid cords.

#### **Carcinoma of the Cervix First Noted in the Puerperium**

CASE 8.—A. R., white, 25 years of age, gravida i, who had no prenatal care, last menstruated on 11/14/42. She was first seen when she was in labor at full term on 8/3/43. A normal baby, weighing 6 pounds, 14 ounces, was born after seven hours and twenty-five minutes of labor. There was no postpartum hemorrhage and puerperium was uneventful. She was out of bed on the sixth day and was discharged the next day. She returned for a routine postnatal examination after eight weeks of puerperium, during which time she had no significant symptoms. A vaginal examination revealed that the entire posterior cervical lip had been replaced by a fungating polypoid mass which was in contact with the posterior fornix, but was not adherent to it. The parametrium was soft without the slightest bit of induration. The corpus was normal in size, shape, position and mobility and there were no palpable masses in the adnexal zones. A biopsy from this mass was misplaced and the patient had six deep x-ray treatments before another was obtained. The histopathologic picture was essentially that of a squamous cell carcinoma of the cervix, which had rudimentary hornification and some giant cells. After 28 treatments for a total of 4,200 r. through six fields, she was admitted to the hospital. At this time, which was almost two months after the first puerperal examination, the only additional finding was a slight fixation of the left parametrium. She received a total of 4,500 mg. hours of radium in three divided doses, and was referred back to the x-ray department for more deep radiation therapy.

#### **The Clinical Picture**

Carcinoma of the cervix is usually small in size at the time of conception. Unfortunately, it may be a silent clinical entity for a long period of time. In the nonpregnant state, one may in a routine or periodic examination occasionally discover the malignancy at a very early stage. During pregnancy, the prospect of an early diagnosis is less likely due to aversion on the part of obstetricians to re-examine

pregnant patients vaginally. Another factor interfering in the diagnosis is a fixed assurance that cervical carcinoma is unlikely to occur. Thus, the growth may virtually become enormous in the last trimester or in puerperium. This was our experience as exemplified in the tabulated clinical data. The only significant symptom attributable to the cancer during pregnancy is *painless bleeding* that occurs in varying amounts. This symptom was only absent in two of our patients, but in six it was found to have been present in variable amounts and with a tendency to recur. It was noted in one patient as a scanty bleeding in the first trimester; in four women in the second trimester, but the real cause remained unsuspected; in one, the bleeding did not develop until she was close to full term; and in one patient, who was admitted exsanguinated and died shortly after her admission. Obviously, carcinoma is too often far from a consideration as a cause of bleeding during pregnancy. In our series, the cause of the bleeding was attributed to erosion two times, and once to threatened abortion. When the true cause of their bleeding was finally determined, their pregnancies had advanced to the last trimester of gestation and the tumor had become very large. Their admittance diagnosis to the hospital at this time was placenta previa.

The cervical changes in all our patients were significant. The degree of cervical involvement noted depended on the period of gestation that the carcinoma was diagnosed. The anterior cervical lip of a patient 10 weeks pregnant was moderately enlarged, and felt very hard. On speculum examination, a small amount of bleeding was seen to arise from a superficial ulceration where the anterior vaginal wall joined the cervix. This tumor diagnosed was the smallest of any in our series. In two cases that were seen in the second trimester of pregnancy but not diagnosed, the cervix was definitely enlarged and appeared beefy and eroded. For those patients who were not diagnosed until the last trimester of pregnancy, the cervical findings usually consisted of a large cauliflower-like mass that had replaced a great part of the cervix, and bled readily on any manipulation. The carcinoma tends to decrease in size in the first three weeks after abdominal delivery. This was noted in two patients, and it is perhaps due to a disappearance of some of the edema and congestion that are present in the cervix prior to childbirth. In five patients (including the one diagnosed in early pregnancy), the parametria were free from induration and grossly would fit into Group 2 (Schmitz). One patient had some parametrial involvement and she would be placed in Group 3, and the patient who was admitted moribund was in Group 5. These growths bled very readily on manipulation, but the discharge was not offensive and necrosis of the neoplasm was not very evident, probably due to the more abundant blood supply during pregnancy.

Thus, from our experience, the two consistent symptoms were painless bleeding and the local vaginal findings. During early pregnancy,

TABLE I. COMPARATIVE CLINICAL DATA

CASE	AGE	PARITY	RACE	PRENATAL CARE	SYMPTOMS DURING PREGNANCY	ADMITTANCE DIAGNOSIS	GESTATION WHEN CA. WAS DIAG.	CERVICAL FINDINGS AND PATHOLOGY	DELIVERY	TREATMENT; SUBSEQUENT COURSE
1 (C. H.)	35	Multip. (5)	White	Began 2½ months	Slight bleeding before and at 1st visit.	For biopsy of cervix.	10 to 12 weeks	Small nodular growth on ant. cerv. lip near vagin. reflection. Nonhornifying squamous cell carcinoma.	Aborted following radiation treatment.	19 x-ray—2,850 r. first 4 weeks. 4,500 mg. hr. radium (3 divided doses); is still receiving radiation. Prognosis is favorable.
2 (L. G.)	33	Primip.	Negro	Began 4th mo. Wassermann positive antiluetic treatment	Hypertension (no bleeding).	Hypertension (nephritis).	7 to 8 months	Moderate sized growth; anterior lip friable, posterior lip indurated. Nonhornifying squamous cell carcinoma.	Fetus dead. B.O.W. rupt. Intrauterine infection. Supravaginal hysterectomy fetus in uterus.	Stomny P.O. course. 69 x-ray treatments 17,275 r. 3,000 mg. hr. radium. Probably died 3½ years later.
3 (L. W.)	31	Multip. (4)	Negro	Began 3 to 4 mo. (outside clinic)	Bleeding erosion in 6th month (was admitted to hosp.)	Labor pains profuse. Bleeding after admission. Placenta previa.	8 months	Large fungating raw area on ant. lip. Infiltrating nonhornifying squamous cell carcinoma.	Porro cerasean.	Uneventful P.O. course. 65 x-ray treatments—10,000 r. Profuse vaginal bleeding 8 mo. later. Died 10 mo. P.O.
4 (B. F.)	32	Multip. (2)	Negro	Began 6 to 7 mo. (outside clinic)	Bleeding erosion at 1st visit.	Bleeding. Placenta previa.	Almost full term	Large cauliflower-like mass in post. lip, infiltrated left parametrial zone. Anaplastic nonhornifying squamous cell carcinoma.	Classical cesarean section. Cervical bleeding persisted at operation.	Cervix packed to stop bleeding. P.O. course rather stormy. Highest P.O. temp. 102.2°; pyelitis on 10th P.O. day. Baby died on 2nd day. Patient uncooperative, and did not return for subsequent treatment as directed.



5 (B. B.)	38	Multip. (10)	White	None	Bleeding— admitted in 5 to 6 mo. as threat- ened abor- tion. Bled intermit- tently.	Bleeding. Placenta pre- via.	Almost full term	Large cauliflower-like mass.  Nonhornifying squamous cell car- cinoma.	Classical cesar- ean section.	Uneventful P. O. re- covery. Tumor mass not affected by radi- ation. Frozen pelvis in 2 mo. 60 x-ray treatments 9,000 r. In terminal condi- tion 9 mo. after de- livery.
6 (A. V.)	38	Multip. (3)	White	Private doctor	None record- ed.	Bleeding prior to ad- mission.	Almost full term	Large cauliflower-like mass.  Nonhornifying squamous cell car- cinoma.	Classical cesar- ean section.	Uneventful P.O. re- covery. 2 mo. later infiltration of recto- vaginal septum. 60 x-ray treatments 7,000 r. Prognosis poor.
7 (M. S.)	43	Multip. (6)	White	None	Bleeding se- vere 4 weeks before ad- mission.	Exsanguin- ated, pro- found shock.	7 months	Large ulcerated mass, infiltrating bladder.  Adenocarcinoma of cervix.		Died undelivered. Massive carcinoma with extension to bladder and metas- tasis to pelvic lymph nodes.
8 (A. R.)	25	Primip.	White	None	None.	Normal labor.	Full term	At postnatal exam. 8 wk. P.P. posterior lip has large cauli- flowerlike mass.  Nonhornifying squamous cell car- cinoma.	Spontaneous delivery.	Still under treatment. Has received 4,500 mg. hr. radium and is getting deep x-ray treatments. Second month after onset of therapy, left par- ametrium slightly infiltrated.

the bleeding must be differentiated from a threatened abortion, or a bleeding nonmalignant erosion. The bimanual palpation of a hard mass that is irregular and bleeds readily should always be followed by a biopsy that might determine the diagnosis. *Any pregnant patient with persistent cervical bleeding should have the same diagnostic biopsy that the nonpregnant patient is accorded.*

### Prognosis

There is a strange divergence of opinion in the medical literature concerning the influence that pregnancy exerts on the growth of cancer of the cervix. Some observers claimed that gestation inhibited the growth of carcinoma of the cervix or at least did not act unfavorably, and based their belief on the ease of operability and the early stage that the neoplasm might be found during a pregnancy (Mankin,<sup>4</sup> Smith,<sup>5</sup> Stöckl,<sup>6</sup> Weibel<sup>7</sup>). On the other hand, some observers contend that local genital hyperemia, increased glycogen content of the genital tissues, and the earlier age of the patient might cause the carcinoma to grow faster. We agree with Danforth,<sup>1</sup> Baer,<sup>2</sup> Brouha and Gosselin,<sup>8</sup> and Nevinsky<sup>9</sup> that the malignancy is not inhibited during pregnancy but possibly accelerated in its rate of growth. Hemorrhage during pregnancy or parturition is a hazard to the patient. If the patient survives the hemorrhage or sepsis, there is the ever gloomy prognosis concerning the growth of the tumor after childbirth. Childbirth trauma is certain to cause the carcinoma to flourish at a greater rate. McNeil<sup>10</sup> has observed that the earlier age group, such as these patients are in, is associated with a greater degree of malignancy of the new growth.

When the diagnosis is made early in pregnancy and is immediately followed by vigorous treatment, a much better prognosis may be expected. Thus, Peham and Amreich,<sup>11</sup> and the tabulated cases in the recent report of Maino and Mussey<sup>12</sup> indicated that a great majority of 5-year or longer cures were found in those patients in whom the diagnosis was established early in pregnancy. In our own limited series, it is obvious to us at least, that patients diagnosed for the first time in late pregnancy had large tumors and despite vigorous therapy that was immediately instituted, their prognosis is poor.

Another factor militating against the ultimate outcome of these unfortunate patients is the delicacy with which the patient is apprised that her condition is serious. In a large clinic, where the social and intelligent strata of the patient are lower, she must at times be informed more directly as to her true condition. Where the patient's feelings are held with delicacy, the patients, such as seen in our clinic, soon lose interest in the inconvenience that the follow-up treatment entails. Our patients move frequently and are soon lost. We feel that the lack of the necessary intensive treatment in three of our patients may thus be explained.

### Treatment

During the past two decades, the swing from radical surgical removal to conservative radiation therapy has received wide recognition. During pregnancy, the treatment is only altered by the problem of the disposition of the fetus. It is felt by many observers that the trauma ordinarily sustained by the cervix, by the mechanics of parturition, may seriously affect the cervix that contains a cancer. Therefore, with the amount of injury being unpredictable where the extent and exact degree of involvement of the tumor is unknown, we prefer to spare the cervix of the trauma of labor. The one patient who had no symptoms during pregnancy, and had an easy labor with no hemorrhage or any sepsis, nevertheless, on her first postnatal visit had a large growth that was in Group 2, and two months later, despite radiation, had become a Group 3 (Schmitz classification).

Those who favor cesarean section in the last trimester of pregnancy may not agree as to the disposition of the fundus. Danforth and Baer would prefer a routine Porro cesarean section because of potential sepsis, and Danforth adds that the possibility of pyometra is obviated. In performing a cesarean section, with or without a hysterectomy, the carcinoma still remains with the patient. Since her ultimate recovery hinges on the therapeutic effect of radium and deep x-ray on the carcinoma in the cervix, profound thought must be given to whether routine removal of the fundus is best for the patient.

The selected manner of abdominal delivery should be one that will facilitate the radium therapy that is given at a subsequent time. A Porro cesarean leaves a cervical stump that is not as effectively treated by radium as a cervix that has a corpus to retain a capsule of radium for crossfire effect. Then again, the bladder assumes a different relationship and may, in being brought over the cervical stump, be involved by radium ray emanation despite its limited field of penetration. Another objection to a supracervical hysterectomy lies in the unpredictability of the histologic extent of the carcinoma. One may cut through malignant cells, or place sutures therein when the cervical stump is closed. It is for these reasons that we prefer an elective classical cesarean section and are in accord with Beck,<sup>13</sup> Titus,<sup>14</sup> McNeil<sup>15</sup> and Schmitz.<sup>16</sup>

We advocate a Porro section when the patient is infected as indicated by the type of vaginal discharge, purulent or not, and the oral temperature of the patient. Thus, the indication for the Porro section is the presence of a known sepsis, not the presence of a carcinoma in itself. Three of our patients had a classical cesarean section. One of them had cervical bleeding that was only controlled by gauze sponge packs, inserted from below. A supracervical amputation of the uterus would not have affected the source of bleeding, and she was in no condition for a complete hysterectomy such as a radical Wertheim (see Case 4).



In general, the treatment we follow is the one Danforth and Baer have proposed, with exception that the uterus should not be removed in the last trimester of pregnancy, except where there is an active intrauterine infection present. Thus, in early gestation, we ignore the pregnancy. We advocate first deep x-ray treatments to irradiate a wide field within the pelvic sphere, and after the death of the fetus, radium to be inserted, giving a total of 4,500 mg. hours, and then to follow up the therapy with many more deep radiations.

When a patient is first diagnosed after the fetus is viable, we favor a classical cesarean section for reasons stated, and as soon as possible in the puerperium start deep radiations; and after involution of the uterus, radium to be given in 1,500 mg. hour doses, giving the patient three such treatments totaling 4,500 mg. hours. The deep radiation was 200 K.V. through six fields and a transvaginal approach whenever possible.

If the patient is reasonably close to having a viable baby, we agree with Baer, who advocates radium therapy first to retard the malignant growth and permit the fetus to attain a viable status before a cesarean section is contemplated.

General supportive treatment is an important phase of the therapy. The diet should be rich in antianemic factor. Where the blood picture indicates an anemia, transfusion is also very helpful. The patient should be impressed with the seriousness of her condition. A well-understanding social service in liaison between the medical division and the patient would be very helpful. The patient's relatives should be apprised of her real condition. The patient should be followed by the social service worker to see that she keeps up her schedule of treatment. Any failure on her part should make the medical or social service agent responsible for informing the patient more definitely concerning the true condition for which she is being treated.

### Summary and Conclusions

Eight cases of carcinoma that appeared in the past five years during a pregnancy were clinically studied. The uneven distribution of these cases, whereby six were noted in one year would render untenable a statistical evaluation of its incidence on our services. Many white and Negro patients are seen annually in our hospital, and it appears that carcinoma of the cervix, at least during pregnancy, might be more frequent in white women. In seven patients the malignancy was a stratified squamous cell carcinoma and in one patient, who died undelivered, it was an adenocarcinoma.

There is a tendency to regard carcinoma of the cervix during pregnancy as so improbable that other causes of bleeding are given stubborn precedence in diagnosis and therapy. The malignancy is thus diagnosed more often toward the end of pregnancy, when the growth has achieved large proportions. Carcinoma of the cervix, contrary to the opinion

of several contributors, continues to develop at a rapid pace during pregnancy. The earlier the diagnosis is established the sooner effective therapy may be instituted, and the better the ultimate prognosis.

The treatment of these cases depends upon the disposition of the pregnancy. In the first trimester the pregnancy is disregarded and deep x-ray therapy is instituted. With the death of the fetus, radium is added to the treatment. In advanced pregnancy, there is added concern for the cervix. The latter should be spared of the injuries that occur during parturition. If there is no infection as noted by the temperature or character of the vaginal discharge, a classical cesarean section is performed to spare the cervix of trauma and to leave intact the fundal portion of the uterus to facilitate the radium therapy, which is started after uterine involution has occurred. A total of 4,500 mg. hours of radium is given in three equally divided doses. As soon after the delivery of the baby as possible, deep x-ray treatments are started, and continued for a long period of time. In the presence of local infection by criteria mentioned, a Porro cesarean section is preferred. In pregnancies close to viability the cesarean section may be deferred, and 1,500 to 3,000 mg. hours of radium may be given to the cervix to temporarily inhibit the progress of the new growth.

The ultimate prognosis for the patient hinges on the persistent continuation of the deep x-ray and radium therapy that is instituted after the disposition of the pregnancy. The patient must be apprised of the seriousness of her condition directly or indirectly. In a public institution, the follow-up is best attended to by a well-established social service department. When the patient fails to adhere fully to the program of the important follow-up therapy, it is the responsibility of the social service department, or the physician to inform the patient more directly of her exact condition.

We gratefully acknowledge the frequent advice and help by Dr. Herbert E. Schmitz of the Department of Gynecology.

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### Discussion

DR. W. C. DANFORTH.—I agree that in most instances the carcinoma is present before the beginning of the pregnancy and do not believe that the essayists need be at any pains to explain the appearance of cancer in the two primiparous women. Carcinoma is not unknown in nulliparas and Miller has pointed out that the incidence in nulliparas does not vary as widely from that of multiparas as many of us have been accustomed to think.

I agree, on the whole, with the scheme of treatment suggested by the authors. In view of the fact that most advanced cancers of the cervix are infected, I should favor cesarean section followed by hysterectomy rather more often than do the essayists. When the cancer is not too extensive, the Ries-Wertheim extended operation may be considered, particularly in the earlier months of pregnancy. In the first trimester, unless the carcinoma is an advanced one, this may be regarded as an excellent form of management. Whether cesarean section only or section followed by excision of the uterus is chosen, the operation should be followed by efficient irradiation, both by means of x-ray and radium. In cases in which the carcinoma is found early in pregnancy, unless complete hysterectomy is chosen, the immediate employment of irradiation, without regard to the pregnancy, is the best treatment. In pregnancy sufficiently advanced that the fetus approaches viability, radium may be used for the purpose of retarding the progress of the cancer until the child becomes capable of extrauterine life. When this is done, as Murphy has pointed out, we must accept some risk of harm to the infant. In an occasional case in early pregnancy, in which the cancer is still in an early stage, total hysterectomy may be considered.

It is highly important that we recognize the danger of allowing delivery through a cervix in which the cancer has grown extensively. To allow the advanced presenting part to force its way through such a cervix exposes the woman to grave danger of hemorrhage because of laceration of the easily injured cervix, and to the certainty, if the patient does not die of hemorrhage, of extension of the cancer and of infection. Cervical incisions and manual dilatation cannot be considered.

Emge, in a paper published in 1934, expressed the opinion upon experimental and clinical evidence, that pregnancy exercises an inhibitory rather than a stimulating effect upon the growth of cancer. I, together with others, have felt that the contrary was probably true, but the number of cases seen by one clinician is too small to permit of a great degree of dogmatism. Stöckl believed that pregnancy neither accelerated nor delayed growth of cancer.

In some of the cases reported tonight, the presence of placenta previa was suspected because of severe bleeding. The likelihood of this confusion between the two has been remarked upon before. The presence of active bleeding calls for a determination of the cause. The essence of the management of carcinoma is early recognition. In view of this, and in the way of friendly and constructive criticism, may I allude to some of the facts of the case histories.

In Case 2, we find that the patient began prenatal care in the third month. At about the eighth month, she was admitted for toxemia. A bag induction was attempted, although it was found that the cervix was "definitely abnormal." At this time, a piece of friable tissue broke off. This was utilized for microscopic study. It is assumed that this procedure was in the hands of an intern or resident. The carcinoma was evidently an advanced one, but, had some one of greater experience recognized the cancer before the introduction of the bag, and had then proceeded to immediate removal of the uterus with the appropriate postoperative irradiation, would not the stormy convalescence have been less likely even though the ultimate result remained the same. The use of the bag is open to the same objections as those already stated when speaking of labor.

The third patient came under observation at the third month. She had frequent spotting and at the sixth month was admitted for suspected placenta previa. In other words, she was bleeding freely. The intern saw what he thought to be an erosion which bled profusely on contact. She was allowed to go home and was admitted at term in labor. At that time, a large carcinomatous mass was found in the anterior lip. The treatment from that point on may be approved. However, at the sixth month, had someone seen her whose gynecologic experience was sufficient to cause him to be aware of the fact that masses in the cervix which bleed easily may be malignant, treatment could have been initiated three months sooner. The marked contrast between the indurated carcinomatous area and the surrounding soft pregnant cervix has been mentioned by Tagliaferro, Sarwey and Bar, and this is in accord with my own experience.

In Case 4, the patient was not seen in the County Hospital until term but a "certified obstetrician" saw her at the sixth month and found an abnormal cervix which bled easily. I assume that "certified" means that he had passed the American Board. Perhaps, in his examination before that Board, the signs of cervical cancer were not discussed. The treatment given her after her admission to the hospital was entirely proper, but the doctor who saw her at the sixth month had an opportunity to do her a real service.

The patient in Case 5 entered the hospital at five months because of bleeding. After a few days' stay she went home, and again I assume that she was seen only by a resident or an intern. At eight and one-half months, she returned bleeding profusely. Again, treatment from this point on was efficient. Had the cancer been recognized at the earlier admission, the terminal condition in which she was when last seen might still have been her fate, but at least her chances would have been better.

It is probable that pregnancy begins in most cases when the cancer is relatively early. In late and far-advanced cancers, pregnancy is much less likely. Treatment is more effective the earlier it is begun. A review of the literature some years ago showed clearly that treatment is more effective in the first six months than in the last three. It is true that the rarity of the combination of pregnancy and cancer may cause the average practitioner to ignore the possibility of such a thing. The present report will help to bring the matter to our attention. It is to be regretted that the residents and interns were seemingly unaware that this combination may occur.

The report will cause all of us to increase our watchfulness. These cases, together with others reported at an earlier meeting of this Society at which this subject was considered, bring the number of cases reported in this city in the past few years to a number which must impress us with the fact that cancer in pregnancy is a complication which cannot be ignored.

In recognition and treatment in the earlier months of pregnancy lies the greatest, and almost the only, hope of cure.

DR. FREDERICK H. FALLS.—About six years ago, Dr. Danforth read a paper before this Society and Dr. Culbertson was asked to discuss it. He said that he could not discuss the paper because he had never seen a case. The President then asked for discussion from the floor, and there was but a handful of men in the room who had ever seen a case of carcinoma of the cervix in pregnancy. Now in a period of five years, according to this paper, eight cases of carcinoma of the cervix uteri and pregnancy have been observed in one institution.

My personal experience has been necessarily very limited. The first patient that I saw was at the University of Iowa. She came in for examination because of bleeding at about the eighth month of pregnancy and was dissatisfied because she was not examined immediately and left. She went to another clinic where placenta



previa was diagnosed, and a classical cesarean section was done. The carcinoma was not discovered while she was in the hospital, but only a few weeks after. She was then sent to our clinic where the diagnosis of carcinoma was confirmed, and she was given radium and x-ray treatment and died within a year.

Another patient with carcinoma came in after an abortion at five months. On examining her, we found a carcinoma which may or may not have been concerned with producing the abortion. This woman was given radium after thorough cauterization of the cervix. The carcinoma was about the size of a walnut. The radium treatment was followed by x-ray treatment. She was alive and in good condition two years after, and then was lost sight of.

The difficulty in managing these cases, it seems to me, hinges on the fact that nobody examined them during early pregnancy. No one recognized the carcinoma. Even with an evident ulcerating carcinoma, it was not recognized. Why should there be this vaginophobia? We do not advocate unnecessary vaginal examinations during pregnancy, but we know a speculum examination of the cervix can be done without danger and that it should constitute a part of every prenatal examination. Examinations should be repeated at any time during pregnancy that symptoms suggestive of carcinoma appear.

The question, of whether a Porro or a classical cesarean section should be done, is important. In one of these cases, several members of this Society were asked their opinion. My opinion was that a classical cesarean section should not be done, because as Whitridge Williams has pointed out, these carcinomas are always infected, and if a classical cesarean section were done, the streptococci and other organisms that were present would invariably produce serious sepsis. Dr. Kobak has now shown that those cases in which a classical section was done, did not develop sepsis. So while this is a very small series, it must be admitted that the *a priori* reasoning that cases will develop sepsis is not borne out by his cases.

There is a very poor prognosis in all of these cases that have progressed so far before treatment. Therefore, the only hope in such cases lies in seeing them very early in pregnancy and doing biopsies in any case in which the merest suspicion exists. Then, disregarding the pregnancy, one should do a total extirpation of the uterus.

The question of whether radium should be used when viability is approached should, I think, receive our attention. It seems to me that there is some danger of injuring the fetus or possibility of stimulating labor and producing abortion in a nonviable child. Since this is true, we feel that it is better to postpone any radiation treatment until the age of viability has been attained and then remove the fetus and the uterus.

This paper is a warning for those responsible for the training of men in both obstetrics and gynecology. If we have residents at the Cook County Hospital who get only obstetric training or residents in other clinics who see no gynecologic patients, we will always have men in charge of cases of this kind who are unable to make a diagnosis. Every obstetrician should be familiar with the course and clinical signs of carcinoma of the cervix.

In the event that the diagnosis is made early, does such a case belong on the obstetric or in the gynecologic ward? I think these cases should be primarily in the hands of gynecologists. As soon as the diagnosis is made, consultation should be asked and the obstetrician and gynecologist should decide what is best to do with that particular patient. If a total hysterectomy is indicated, she should be transferred to the gynecologic service. If a cesarean section is to be done, she should be retained in the obstetric service and be transferred a few days after delivery.

DR. RALPH A. REIS.—I would like to ask Dr. Kobak what the fetal salvage was in this series. He did not mention it in the paper.

I would like to emphasize what Dr. Falls said about so-called vaginal examination "phobia." In the last year, it has been my experience to see three patients taken to the operating room at the eighth month because of painless bleeding. One had a ruptured vulvar varix, a second had a polyp in the cervical sulcus and was not examined until very intensive bleeding appeared. I want to raise the question, whether it is not the feeling of most of us that a vaginal examination carefully done even in the face of threatening abortion can be kept a harmless procedure? I know two men in the group Dr. Danforth calls conservative, who will not examine a patient vaginally for fear the patient will miscarry. I do not think we can do intelligent obstetrics without a vaginal examination. If we cannot do that without causing abortion, then we do not belong in this specialty.

DR. J. E. FITZGERALD.—There seems to be some misapprehension as to the reason for presenting these statistics. I am sure you will agree that the principal reason for calling the attention of the profession to the occurrence of carcinoma of the cervix in pregnancy is that these cases are not diagnosed and for the reason Dr. Reis has given. If you will take Dr. Danforth's statistics on the incidence of carcinoma during pregnancy, there should be twenty cases in Chicago a year. If you accept Dr. Baer's idea (1:10,000) there should be six. Of the twenty cases that should have occurred last year, I am sure that most of them were not found. They were not found especially for the reason Dr. Reis gave.

There has been some criticism of the residents and interns. Having been told not to examine pregnant patients vaginally, the residents and interns do not do it. We have told residents and interns not to make vaginal examinations in a pregnant woman because an abortion or infection might result. We are perfectly convinced when we see a group as large as this in one year, that there are many carcinomas of the cervix that occur during pregnancy, and that the diagnosis is not made because of our fear either to do a vaginal examination, or to insert a speculum and find out why the patient is bleeding. Our reason for presenting these statistics is to see if more and more of the profession will not adequately examine pregnant women who are bleeding from the cervix, and thus give some help in the diagnosis of possible carcinomas.

DR. J. ROBERT WILLSON.—Since 1931, there have been six cases of carcinoma in pregnancy treated at the Chicago Lying-in Hospital. Four of these were diagnosed in late pregnancy and two in the puerperium. Only four occurred on our service, the remaining two being referred. During that time, there were approximately 45,000 deliveries, so the incidence of carcinoma of the cervix developing in pregnancy is 1 in 10,500 cases.

Four of the patients were treated more than five years ago, and are therefore eligible for the five-year survival statistics. Of this group, two or 50 per cent, survived at least five years. One had an early lesion and was treated by radium applications and deep x-ray therapy post partum. She is alive and well with no evidence of recurrence. The second patient who lived longer than five years was treated by predelivery radium and postdelivery x-ray therapy. She survived seven and one-half years, and died subsequently with an extensive malignant growth which was slowed down but not completely stopped by the treatment. Two of the patients lived less than five years. One refused treatment and survived twenty months. The other patient survived seven and one-half months after treatment was begun. The fifth patient was treated one year ago, and at this time, there is no evidence of extension of the initial lesion. The sixth patient is under treatment at present.

DR. KOBAK (closing).—The primary purpose of this paper was to show the pitfalls in diagnosis of a carcinoma during pregnancy. In the early months of gestation one finds the neoplasm is smaller, and therapy, radiation or surgical, is more likely to be successful. In the recent report of Maino and Mussey one finds support to this contention.

The superiority of radiation over surgery in treating carcinoma of the cervix has been shown in many clinics. The late Dr. Emil Ries, who was very skillful in the performance of the radical Wertheim operation, conceded before this Society that radium therapy was superior to radical surgery. We believe that this also holds for carcinomas that occur concomitant with pregnancy.

In our case reports errors that are very obvious in a posteriori reasoning are much in evidence. These mistakes were made by doctors not on the staff of Cook County Hospital as well as by our residents. The latter, as pointed out, did so by adhering to the popular phobia of vaginal examination, or regarded the malignancy as too improbable for a diagnosis.

Dr. Danforth referred to the patient who had a septic course. At no time did this patient present any symptoms or findings that could give a clue that a carcinoma was present in the cervix. Speculum visualization was apparently negative and there was no bleeding at any time. Her problem appeared to be the hypertension. When the fetal heart tones disappeared and several attempts at medical induction failed, we felt that the uterus must be emptied because of the persistently high blood pressure. Metreuryesis was contemplated, but when the resident found the cervix to be abnormal it was not carried out. True, the bag of water ruptured, a pulseless cord prolapsed, and sepsis followed, but all this was unpredictable. The bag was, therefore, not inserted into the uterus.

Fortunately we always examine every suspect placenta previa vaginally. We thereby discovered the presence of carcinoma, although unfortunately late in the pregnancy. One of two patients, who had no bleeding at any time, was only diagnosed after an uneventful labor, when a postpartum examination was made.

In preferring a classical cesarean section as a means of interrupting the pregnancy prior to the radiation, we concur with Beck, Titus, McNeil and Schmitz.

Concerning the fetus, it was shown by Strauss that 20 per cent of patients whose cervix was irradiated prior to cesarean section had a microcephalic fetus.

Concerning the fetal salvage, seven mothers had a pregnancy that extended beyond seven months. One died undelivered. One baby died in two days of bronchopneumonia and *B. pyocyaneus* was found in the lung tissues. One was still-born. The four remaining babies had an uneventful course.

## ANDROGENIC THERAPY IN MALIGNANT DISEASE OF THE FEMALE GENITALIA\*

### Preliminary Report

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### Introduction

IN AN extensive laboratory study of gonad hormones in 1932, Moore and Price postulated their conception of hormone interactions to include four principles: (1) Gonad hormones stimulate homologous accessories; (2) Secretions produced by the pituitary stimulate the gonads to function both in germ cell production and in hormone secretion; (3) Gonad hormones have no *direct* effect on the gonads of either the same or the opposite sex; (4) Gonad hormones of either sex exert a depressing effect upon the pituitary which results in a diminished amount of the sex-stimulating factor available to the organism.

Although some laboratory work<sup>1-5</sup> suggestive of a possible gynecogenic effect of testosterone has been reported since the above conceptions were established, most of the work has been confirmatory.<sup>6-11</sup> Salmon<sup>12</sup> after making a comprehensive survey of the literature relative to the effects of androgenic therapy in laboratory animals, points out the contradictory and paradoxical effects obtained by various investigators. He concluded that the application of laboratory results to the human female should be made with caution. After conducting a rather extensive clinical investigation, Salmon has postulated that the therapeutic effectiveness of testosterone propionate in gynecology appears to stem from the following properties: (a) Its ability to inhibit the gonadotropic activity of the hypophysis; (b) to suppress or decrease estrogen production; (c) to nullify or modify the activity of the gynecogens; (d) to inhibit the proliferative processes in the endometrium; and (e) to inhibit the reactivity of the uterine musculature. Thus our clinical concepts, postulated by Salmon and generally accepted today, relative to pituitary and gonad therapy are not dissimilar to the conclusions reached by Moore in his laboratory study.

The urologists have carried these concepts into clinical medicine in their treatment of prostatic carcinomas. It has been well established during the last few years that the estrogens are of definite value in the treatment of carcinoma of the prostate gland. There has been prompt relief of pain and urinary symptoms with regression of prostatic lesions as determined by rectal palpation. There has been, in addition, regression of lymph nodes and of metastatic bone lesions as seen by repeated

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x-rays.<sup>13</sup> Pathologic studies have revealed actual regressive changes in the cytoplasm and nucleus of tumor cells.<sup>14</sup> These effects are presumed due to suppression of pituitary function by the estrogenic material which exerts little or no stimulating effects on the male secondary sexual organs. The estrogenic (or androgenic) suppression of pituitary function has been worked out clinically and in the experimental laboratory. In animals both the basal metabolic rate and weight of adrenal glands are decreased by administrations of estrogens. The growth of immature animals is also inhibited. Urinary excretion of the pituitary follicle-stimulating hormone is decreased with administration of estrogens (or androgens).<sup>15-17</sup> Indeed, the rationale of hormone therapy in the menopause is based on the inhibition of the gonadotropic pituitary factor by estrogens (or androgens) when, with progressive ovarian failure, the unopposed action of the gonadotropic hormone produces symptoms.

In the light of these laboratory and clinical studies and in view of the successful application in clinical urology of the conceptions established thereby, an investigation of the possible value of male hormone in the treatment of malignancies of the female genital tract seemed highly warranted. If by the administration of testosterone the depressing effect on the pituitary would diminish the amount of sex-stimulating hormone, and if such administration is without effect upon the heterologous secondary female organs, it seemed not unreasonable to believe that retardation, even possible regression of the malignant growth might occur in a manner comparable to the effect of estrogens on prostatic growths.

A finding of speculative interest in this connection was first pointed out by Aschheim and Zondek, when they found a positive reaction of their pregnancy test in cases of genital malignancy (uterus, ovaries, testes). This has been confirmed by many. No appreciable increase in pituitary gonadotropic factor has been found in the urine in nongenital malignancies and the relationship between the genital growth and the associated increase in urinary gonadotropic hormone in such cases is one of interest. Saphir<sup>18</sup> has postulated that a positive A-Z test in genital malignancy may be due to a destruction of genital function stimulating castration. This hypothesis, however, would seem not to explain satisfactorily the positive reaction obtained in carcinoma of the uterus, where no known destruction of ovarian function has occurred. The possibility that the increase in gonadotropic hormone may be the cause rather than the effect of the genital malignancy suggests itself. If such is the case, administration of testosterone with the resultant depression of pituitary hormone would again seem logical and warranted.

#### Material and Method

It became apparent immediately that the task of selecting clinical material for such a study was fraught with difficulty. To withhold for experimental purposes any of the accepted modes of treatment to pa-

tients with early carcinoma was, of course, wholly unjustified. Moreover, the administration of testosterone to such patients following surgery or coincidentally with irradiation would make the evaluation of clinical results extremely difficult. We were forced, therefore, to reserve hormone therapy for those patients who failed to respond to orthodox forms of treatment, and for whom it was felt, nothing more could be accomplished. With such criteria for the selection of material, studies were begun on a most discouraging group of patients. Cases were selected from the Northwestern University Clinics and from the private gynecologic service at Passavant Memorial Hospital including carcinomas of the uterine corpus, cervix, Fallopian tube, ovary and breast.

A somewhat generous dose of testosterone propionate was arbitrarily chosen with the thought of "nothing to lose, everything to gain" in these patients. One hundred and forty to 150 mg. weekly were given either as oreton—M, in which case two 10 mg. tablets were taken daily by mouth, or as oreton, in which case the patient received three 50 mg. injections per week intramuscularly.

### Case Histories

Our first five patients, including three carcinomas of the cervix and two carcinomas of the corpus, have been receiving testosterone propionate for ten months. During this period, each patient has received more than 6,000 mg. of testosterone propionate intramuscularly. Following is a brief outline of the history and progress of each of the original five patients, with which this preliminary report is chiefly concerned.

CASE 1.—(A.S.) This 39-year-old patient first appeared in the Northwestern University Clinic on November 9, 1939. She had had slight vaginal spotting for one week, and a biopsy done at the Chicago Tumor Clinic had revealed an early carcinoma of the cervix. Five days later, examination under anesthesia at Passavant Hospital revealed an endocervical carcinoma between 8 and 12 o'clock.

Radium was placed intrauterinely in chain tandem and interstitially about the lesion for a total dose of 3,500 mc. hours. The patient developed some necrosis of the cervix, with discharge, vaginitis and rather marked pelvic cellulitis. There was marked induration in the right broad ligament and in the region of the bladder anteriorly. There were some urinary symptoms (frequency, pain, urgency). Cystoscopy and 4 pyelograms revealed edema but no metastases or intrinsic pathology. This cellulitis and induration lasted approximately 9 months (until September, 1940). The first course of x-ray (7,000 r.) was given from 11/20/39 to 2/19/40.

In October, 1940, pelvic examination revealed marked thickening anteriorly to the left and patient was started on a second series of deep x-ray (7,450 r.).

The patient complained of swelling of both lower legs in July, 1941, and in October, 1941, a heavy mass was felt anteriorly and to the left extending to the pelvic wall. Our impression at this time was recurrent carcinoma.

The patient's condition remained stationary and in February, 1942, induration high in the left pelvis was felt with edema of the abdominal wall. This was thought to be the result of gland involvement. Pelvic

examination in May, 1942, revealed persistent induration in the left broad ligament, extending to the ilium. It was nodular.

Examination on January 27, 1943, revealed areas of brawny edema in the left lower quadrant of the abdomen and groin, brawny thickening in the left broad ligament, and a golf ball-sized area of stony hard induration high in the right broad ligament. The cervix was smooth and closed. A third course of deep x-ray therapy (9,000 r.) was given.

On March 10, 1943, rectovaginal examination revealed perirectal nodulations. On 4/7/43 there was edema of both legs and thickening of both broad ligaments.

The first injection was given on 4/9/43. The clitoris began to hypertrophy after a month's treatment, and by 5/19/43 was about four times its original size. Tissues were succulent at this time and have remained so. Vaginal smears have shown moderate cornification.

There has been occasional itching of the skin, but no acne has been manifested. Patient states that her hair is oily and that she has to wash it more often. She began first to notice a beard on May 30, and while it has gradually increased, it is bothersome only on her upper lip. There has also been some increase in leg hair. There have been no breast changes.

During the early part of June, this patient's voice began to deepen and occasionally to crack. This voice change has become progressively more noticeable to both the patient and to us.

Her weight was 218 pounds at the onset of treatment and is now down to 200 pounds. After approximately two months of treatment she became most anxious to lose weight and has been on a voluntary reduction diet since.

On 6/11/43, this patient voluntarily reported that the treatments had markedly increased her sexual desires. She reported an extreme feeling of well-being bordering on euphoria. This increase in libido has been a constant factor. It is still on the increase. Before treatment patient had intercourse once a week or even less, and now has it four times a week. She is wondering whether that is too much.

X-rays of the long bones, skull, and pelvis have revealed no evidence of metastases. Blood chemistry after 6 months' treatment revealed: N.P.N.—36.8; creatinin—1.61; cholesterol—242; calcium—9.1; phosphorus—2.75; phosphatase—4.35; total protein—7.8. Pelvic examination at the end of October, 1943, revealed less broad ligament thickening and the patient seemed to be improved.

CASE 2.—(J. T.) This 60-year-old patient first reported to the Northwestern Clinic in December, 1941. Her history included intermittent vaginal bleeding during the previous three years (15 years after the menopause). These episodes of bleeding were often accompanied by back pain, and did not feel like her menstrual periods previously. Pelvic examination on December 8, 1941, revealed atrophic tissues and a blood tinged vaginal discharge. The cervix was small, smooth, and mobile with a dark bloody ooze coming from the os. The corpus was not outlined on bimanual examination. John Clark test was markedly positive and revealed the canal to be 7 cm. in depth. A diagnosis of carcinoma of the corpus was made and the patient was sent to Passavant Hospital.

On curettage (December 11, 1941), much necrotic, carcinomatous tissue was obtained. Because of the patient's age, obesity, and medical contraindications, radium was chosen in preference to hysterectomy. She received her initial radium treatment on December 11, 1941, a total

dose of 2,800 mc. in the uterine cavity. The microscopic report was adeno-acanthoma of the corpus. Patient received her first course of deep x-ray, a total of 8,350 r. from December, 1941, to March, 1942.

On March 18, 1942, the patient was seen in Northwestern Clinic, complaining of watery discharge. John Clark test was negative. The cervix was open and there was no retained fluid in the uterus. Watery discharge continued and the patient developed lower abdominal discomfort. There was essentially no change in the patient's condition and on July 8, 1942, she was sent to Passavant Hospital for re-evaluation. At this time, a moderate hydropyometria was found with slightly more bleeding than normal. Slight tissue was obtained with occasional suspicious groups of cells seen; no radium was given.

Examinations remained negative during the autumn of 1942, although the patient complained almost constantly of discomfort in the lower abdomen.

On February 2, 1943, curettage at Passavant Memorial Hospital revealed tissue which was definitely adenocarcinomatous on microscopic examination. There was the impression of a friable mass in the right horn of the uterus. A second intrauterine radium treatment was given; the total dose 2,450 mc. hours.

Patient complained of abdominal discomfort during the summer of 1943. She has had broad ligament thickening bilaterally and some obvious necrosis of the cervix presumably the result of radium treatment. Differentiation between extension of the malignant process and post-irradiation reaction has been most difficult in this patient.

Testosterone injections were begun on April 14, 1943. The clitoris has hypertrophied to approximately four times its original size. The vulvo-vaginal tissues have not been particularly succulent. Vaginal smears have shown no estrogenic effect and cells have been characteristic of atrophic vaginal tissues with slight tendency to mucinification.

There have been no changes in the texture of the skin and no breast changes. Slight acneform eruptions appeared on the face at the onset of treatment but soon disappeared and have not recurred. This patient had a tendency toward facial hirsutism prior to treatment and has now developed a marked beard involving the cheeks, chin, and upper lip.

After five weeks of treatment, the patient began to complain of hoarseness. This complaint has been constant and her voice has become progressively deeper.

Her weight at the onset of treatment was 185 pounds, and during the first six months, she gained approximately six pounds. At present, the patient is slightly under her initial weight.

There has been a marked increase in this patient's sexual desires. This increased libido first became noticeable during the last part of May. Prior to treatment, the patient had had no sexual intercourse for two years because she was "too sore." She now has intercourse approximately two times a week and has repeatedly suggested that her husband receive some of the medicine also.

X-rays of the long bones, skull and pelvis have revealed no evidence of metastases. Blood chemistry after six months' treatment revealed: N.P.N.—35.8; creatinin—1.25; calcium—9.6; phosphorus—3.49; phosphatase—2.15; total protein—6.42. There has been much controversy relative to the evaluation of the broad ligament thickening, necrosis, and bleeding which this patient has manifested during the last two months (October and November, 1943). It has been practically impossible to



tell whether the findings in this patient have been on the basis of an extension of her malignancy, or on the basis of postirradiation reaction. While the patient remained cheerful during the first five or six months' treatment, she recently felt somewhat depressed and has had rather severe lower abdominal discomfort.

CASE 3.—(M. B.) This 53-year-old divorcee was first seen by us in the clinic in June, 1936, over seven years ago. She had been having some blood-tinged vaginal discharge with some free bleeding as well. Pelvic examination revealed a large granular cervix which bled easily on examination. The involvement was chiefly of the anterior cervical lip. There was a freely movable bean-size tumor in the vaginal mucosa, one inch below the cervix in the midline. The uterus was retroflexed and of normal size. Attempts to move it were painful. Clinical impression was carcinoma of the cervix. Tissue was taken for biopsy and microscopic examination confirmed our impression of carcinoma. Patient was given 4,000 mc. hr. of radium interstitially in palisade arrangement and in canal. The bean-sized vaginal tumor was also removed. She received a course of deep x-ray (5,000 r.) from July to October, 1936.

Her course was followed in the Gynecological Dispensary and aside from some sloughing of the cervix with discharge was perfectly satisfactory. Pelvic examination on March 3, 1937, showed the cervix to be shrunk and fibrous, with still some watery discharge. There was no infiltration in the broad ligaments or rectovaginal septum. In July, 1937, the impression was one of clinical arrest. There were no complaints referable to the pelvic problem and the patient was followed in the arthritis clinic for some time. Five years after this impression of clinical arrest, the patient developed a Virchow nodule in the left supraclavicular space; biopsy proved it to be squamous cell carcinoma. Impression was then retroperitoneal metastasis. The situation was explained to the patient and arrangements were made to have the services of a local physician.

Testosterone injections were begun on April 14, 1943. Marked hypertrophy of the clitoris was evident by the first of June, and the tissues have been succulent. Vaginal smears are suggestive of mucinification.

After fifteen treatments, the patient began to complain of acne which first appeared on her chest, later on her back. There was only slight facial involvement. The skin involvement has gradually cleared up and has not recurred. A beard was first noted during the first part of June and has increased gradually. It is particularly noticeable on the upper lip and under the chin. Patient has noted no changes relative to the hair on her head but says that there is an increased amount of pubic hair. She has had the impression that her skin has been a trifle drier. There have been no breast changes.

Patient first reported a voice change about the middle of June; it has become progressively deeper since that time.

This patient's weight, approximately 143 pounds at the beginning of treatment, had remained fairly constant until nine weeks ago. Patient has lost eight pounds in the last nine weeks.

Increase in libido was first reported after a month's treatment. It has progressively increased to date. This patient, although not married now, inquired whether or not intercourse would harm her. She felt something must be done about her increased sexual desires.

At the beginning of treatment, this patient was extremely discouraged, but as time went by, she became more and more cheerful. Re-

cently, pain has developed in the extreme lower back and right hip, radiating down the right leg. Bimanual pelvic examination had remained negative until October, 1943, when some suggestion of extension high on the right was discovered. Blood chemistry after six months' treatment revealed: N.P.N.—36.8; creatinin—1.63; calcium—10.3; phosphorus—4.59; phosphatase—2.67; total protein—7.96

During the course of treatment, the metastatic mass in the left supra-clavicular region became progressively larger and more painful. Only recently, after x-ray therapy, has there been a marked decrease in the size of this tumor. This patient has maintained her cheerful attitude.

X-rays of the long bones, skull and pelvis taken during the last week in August were reported as negative relative to metastases. After repeat films on November 5 showed obvious metastases, a review of the August films (and also some made in June) revealed the bony involvement to be present all through the series. The metastatic lesions are evidently progressing.

CASE 4.—(R. G.) This 45-year-old patient first reported to the Northwestern University Clinic on October 28, 1942, with complaints of continuous vaginal bleeding of two months' duration and right lower quadrant abdominal pain, which was severe and throbbing in nature.

She gave a history of similar complaints in May, 1939, at which time she was seen in another hospital. A curettage was made on May 14, 1939, and microscopic examination of the curettings revealed adenocarcinoma of the body of the uterus. The patient received two treatments with radium while in the hospital, the total dosage unknown. A course of deep x-ray was given. Following this treatment, the patient was asymptomatic until January, 1942, when she bled for two months. There had been no flow between May, 1939, and January, 1942. A second course of deep x-ray was given. There was no bleeding from March, 1942, to September, 1942, when it again occurred. There was continuous vaginal bleeding from September 1, to her first clinic visit on 10/28/42. The right-sided abdominal pain began again some five weeks prior to this visit. Pelvic examination on 10/28/42 revealed a pelvic mass the size of a 2½ months' pregnancy replacing the uterus with massive infiltration in the base of the right broad ligament and none on the left.

The patient entered Passavant Memorial Hospital the middle of January, 1943, for evaluation. Examination under anesthesia revealed a hopeless recurrence of malignancy with extension into both broad ligaments. Curettings revealed typical adenocarcinoma. Further treatment seemed hopeless and the family was informed of the patient's condition. When seen about a month later in the Northwestern University Clinic, the patient had been bleeding a great deal and there was no change in the degree of pelvic extension, it was extremely marked. Arrangements were made for terminal care.

Definite hypertrophy of the clitoris appeared after five weeks' treatment with testosterone which was begun on April 1, 1943. The clitoris has become roughly four or five times its original size. Tissues have been moderately succulent. Vaginal smears have revealed a picture suggestive of atrophy.

There has been no acne. Skin texture has been unchanged. The patient states that with the onset of treatment, her hair came out in appreciable quantities when combed. This has been less noticeable recently. The patient had developed a beard, particularly marked on her

upper lip. However, facial hirsutism has been of lesser importance here. There have been no breast changes.

Patient began to complain rather strenuously of hoarseness the last part of May, and states that her voice has become progressively deeper since. Voice change has been particularly striking in this patient.

At the onset of treatment, this patient weighed 100 pounds. There has been an increase of weight during the last six months of slightly more than 20 pounds. However, a marked edema of the legs, particularly the right, was present and may be in part responsible for the weight increase.

This patient was quite depressed at the onset of treatment, had no appetite and apparently realized the hopelessness of her condition. The improvement in morale has been striking. She has become increasingly more cheerful and after six to eight weeks of treatment felt well enough to work again. She has found a position and is still working, nine months after terminal arrangements had been made. Although she has not had a husband for some time and had thought nothing of matters of sex for a long time, she offered information relative to her increased libido on interrogation.

X-ray of the long bones, skull and pelvis revealed no evidence of bony metastases. Blood chemistry after six months' treatment revealed: N.P.N.—39.4; creatinin—1.33; cholesterol—2.80; calcium—9.4; phosphorus—3.09; phosphatase—4.96; total protein—7.95.

In November, 1943, pelvic examination revealed no change in the marked induration throughout the pelvis. The edema of the legs, so massive during the last few months, is improved.

CASE 5.—(S. S.) This 49-year-old patient was first seen in the Northwestern Clinic in December, 1932. She was complaining of a bleeding on trauma and between periods, and examination revealed a "precancerous" leucoplakic cervix. Biopsy was recommended but not done. The patient was not seen again until 10/10/34, when she reappeared with a complaint of bleeding daily between periods for two weeks. Biopsy revealed carcinoma of cervix and patient received 4,000 mc. hr. of radium interstitially and into bases of broad ligament by coincident surgical exposure on 11/14/34. Deep x-ray therapy for a total of 5,200 r. was given from December 13, 1934, to February 16, 1935. Broad ligament thickening and cervical obstruction with pyometra resulted. There was also some postradiation cystitis. The induration in the deep right pelvis was very marked through the summer of 1935, and another course of deep x-ray for a total dose of 2,600 r. was given. The process was thought to be extension and the prognosis was given as poor. During the fall and winter of 1935 and 1936 the patient began to improve; she gained weight and the induration gradually decreased. Then on September 2, 1936, there was thought again to be marked extension into the right broad ligament. Another 2,800 r. of deep x-ray was given. On April 7, 1937, there was no further extension and the induration of the right broad ligament was not felt to be advancing.

Pain and edema began to appear in the right leg in August, 1942, and gradually increased. In October, 1942, a one-inch swelling to the right of the cervix between it and the bony pelvis was felt. In March, 1943, stony hard induration was felt between the cervix and the bony pelvis on the right. It was decided to give the patient testosterone because of her poor prognosis.

Treatments were begun in April, 1943. Hypertrophy of the clitoris began after about five weeks' treatment. The organ is now about three

to four times its original size. The vulvovaginal tissues have been less succulent here than in the other patients. Vaginal smears have shown mucinified cells.

During the first two months of treatment, there was some acne on the face and chest. This cleared rapidly and there has been no recurrence. A beard developed after six weeks. The patient at first bleached the hair, but recently has been forced to shave. There has been some increase in leg hair.

The patient has been complaining of voice changes since about the middle of June, 1943. This is particularly marked in the morning. Objectively, her voice is extremely husky and cracks frequently. She states that she can no longer sing.

The patient's weight has been constantly between 170 and 175 pounds.

This patient continues to feel extremely well and except for slight edema of the right leg has no symptoms. She has been considering remarriage for several years, and finally consented after two months' treatment. Libido has been greatly increased.

X-rays of the long bones, pelvis, and skull are all negative. Blood chemistry was as follows after six months' treatment: N.P.N.—37.8; creatinin—1.3; cholesterol—302; calcium—9.3; phosphorus—2.12; phosphatase—2.85; total protein—7.45.

There is little change in the findings on bimanual examination.

### Observations and Discussion

The final evaluation of a study such as we have undertaken requires much time. The clinical course of each patient must be observed carefully for a long period and must be followed up by any pathologic data which may ultimately become available. Because the final chapter in each case may not be written for some time, and because of the several interesting clinical observations already made during the course of treatment, this preliminary report seemed merited. This initial report deals primarily with our five original patients although occasional reference to subsequent patients is made.

Among the early changes noted were those manifested in the vulvovaginal tissues. A constant finding in our original group, and one which has been observed in most but not all of our subsequent cases has been hypertrophy of the clitoris. This observation has frequently been reported by others during therapy with testosterone when the dose has exceeded 250 to 350 mg. per month. Enlargement of the clitoris in our patients who have received slightly in excess of 600 mg. per month has been observed to begin after about four or five weeks of therapy and has progressed until in most cases the organ has reached up to four times its original size.

In most cases the tissues have remained somewhat succulent and appear somewhat engorged. They are not atrophic as one might expect in patients who have received large doses of x-ray and radium.

The reports in the literature relative to the effect of male hormone therapy on the vagina as evidenced by the vaginal smear are conflicting. Deanesly and Parkes<sup>5</sup> in 1936, working with immature, ovariectomized,



and adrenalectomized rats concluded that testosterone had a direct effect on the vagina manifested by opening of the canal with cornification. Nathanson and Towne<sup>15</sup> noted a profuse vaginal discharge in four patients following injections of testosterone and found that the discharge consisted in part of cornified cells. All four patients showed an estrogenic effect on the vaginal smears. Two had complete cornification. However, other workers, working together and independently have reported a transition to an atrophic, menopausal type of smear following large doses of testosterone. There was a gradual replacement of the usual large squamous epithelial cell types characteristic of the normal cycle by smaller, rounder, and more compact cells with large, well-preserved nuclei.<sup>19-22</sup>

In only one of our patients (Case 1, A. S.) has there been any evidence of cornification. The estrogenic effect in this case was moderate and vaginal smears have changed very little since treatment was instituted. Vaginal smears made on the remainder of our original group have consistently shown small, round cells with large nuclei similar to those reported by Papanicolaou, Ripley, and Shorr.<sup>19</sup> The picture has been varied between mucinification and atrophy.

In his discussion of androgenic therapy in gynecology, Salmon,<sup>12</sup> after amplifying his initial studies, concluded that the vaginal smear effects varied with the dose of testosterone propionate administered. In his group an estrogenic type of smear was obtained only when concentrated courses (50 to 100 mg. per day) of testosterone propionate were administered for at least three weeks. Even 25 mg. dose daily for many months did not produce this estrogenic-like action. This concept perhaps explains the varied results obtained by different investigators and certainly is consistent with our findings.

A beard has appeared in nearly all our patients in from four to six weeks and has become increasingly more marked with continued treatment. Although, at first, in some cases bleaching sufficed to minimize the unfavorable appearance caused by this facial hirsutism, all of our original patients have resorted to using a razor. There has been some increase in the amount of hair on the legs in two cases and in one patient the amount and extent of pubic hair has definitely increased. Although one patient reported early in the course of treatment that her hair was falling out in large quantities on combing, this soon ceased and all in all there have been no remarkable changes in the cranial hair.

Three of our original five patients complained of acneform eruptions during the first two months of treatment. These eruptions appeared on the chest, back, and face. Although bothersome to the patient, this condition has been transient in each case and has occurred in many of our subsequent patients. Generalized itching has occurred from time to time in one patient, but skin changes have otherwise been negligible. No breast changes have been observed.

One of the most striking manifestations of treatment and one of the most distressing to the patient has been change in voice. This first began to appear in from four to six weeks, concomitantly with the enlargement of the clitoris and appearance of a beard. In some instances, the voice has become quite masculine in depth and in most cases has become harsh and rasping in quality, cracking frequently in the course of conversation. This hoarseness, as the patient subjectively describes it, has been perhaps the most bothersome of the undesirable side effects noted in the course of treatment.

Probably the most encouraging observation noted in our group early in the course of treatment has been improvement of morale. There has been a definite feeling of well-being bordering at times on euphoria. There has been a marked change in mental outlook, for the most part, from one of hopelessness prior to injections to one of cheerfulness. It has been recognized for some time that symptoms of the menopause can be controlled by administration of androgens and this may be in part the explanation for the improvement seen in these patients in whom menopause has been induced by radium and x-ray. Certainly less fatigue, less nervousness, and in most cases fewer flushes were noted after injections were under way.

Associated with the progressively increased feeling of well-being has been a definite and consistent increase in libido. This has been constant in our original group and in essentially all of our subsequent cases. It has been marked enough in most instances to elicit voluntary information from the patients relative to matters of intercourse. For instance, Case 1 (A. S.) has increased the number of times she has intercourse per week from one to four and has asked if more would be harmful; Case 2 (J. T.) has resumed intercourse after a 2-year lapse, is having relations twice a week, and has several times inquired as to the possibility of her husband receiving injections; Case 3 (M. B.), although no longer living with her husband, has asked whether or not intercourse would harm her because her sexual desires have become intolerable; Case 5 (S. S.) had been considering remarriage for several years, and finally wedded after two months' treatment, acknowledging a marked increase in her sexual desires; Case 4 (R. G.), although not voluntarily offering any information, readily admitted on direct questioning, her libido was increased.

These observations were of particular interest to us in the light of conflicting reports in the literature. Salmon,<sup>12</sup> in his fore-mentioned study, reported that many of his patients experienced a definite increase in libido during the course of injections and for several weeks thereafter. The majority of his cases received more than 500 mg. of the hormone in one month. The clitoris in many of these women became hyperemic and very sensitive to touch. These results were essentially the same as in our group. Greenblatt, Mortara, and Torpin,<sup>23</sup> using pellet im-

plantation of testosterone propionate in varying dosage, likewise reported a resurgence of libido in almost every one of 55 patients, who once had had normal sexual desires.

However, Silberman, Radman, and Abarbanel,<sup>24</sup> using smaller doses of 5 mg. two to three times per week, were able to control menopausal symptoms in 15 patients, but noted no change in libido. Interestingly enough, Rubenstein, Shapiro and Freeman<sup>25</sup> have reported successful relief in five women suffering from abnormally strong sexual desires by the administration of 25 mg. of testosterone propionate at varying intervals. Since the exaggerated sex urge in these patient was definitely associated with premenstrual tension and since such tension has been successfully treated by testosterone propionate, relief may have been on this basis. However this may be, there is certainly no question as to the increase in libido in our group.

Particularly worthy of emphasis among our observations are: (1) feeling of well-being approaching euphoria at times, (2) improved appetite (some of our subsequent patients have notably gained weight), (3) control of menopausal symptoms (viz., depression, nervousness, insomnia, and to a lesser degree flushes), and (4) increased libido. These findings have been consistent and gratifying and of themselves seemingly justify our efforts. The masculinizing effects of our large doses of testosterone have been definite, but in most instances readily accepted by the patient as secondary to her improved physical and mental well-being. The realization that something is being done for them coupled with subjective improvement has apparently minimized the untoward masculinizing symptoms, and has offered new hope to these unfortunate patients. Their cooperation and faithfulness in keeping appointments have been truly remarkable.

On the other hand, there is nothing to indicate that there has been any regression of the malignant process in any case. Indeed, in one case (Case 3, M. B.), there is definite evidence that the growth has progressed during treatment. The metastatic supraclavicular mass became increasingly larger until x-ray was given and repeated x-rays of the long bones have shown progression of the bony metastases during the last five months. Although it is true that the remainder of our original group (particularly Case 4, R. G.) have done well in the light of their prognosis prior to the onset of treatment, any retarding effect on the cancerous growth remains unestablished. The effect of treatment upon the malignant process will be difficult to evaluate, will require much time, and should include the study of any pathologic data which may ultimately become available.

Varying the dosage of testosterone seems indicated. It is possible that the desirable symptomatic results above described may be obtained with a smaller dosage which would eliminate the masculinizing effects. This is being done in some of our subsequent patients.

### Summary

A series of patients with previously treated but progressively advancing malignancies of the female genitalia have been given testosterone propionate in arbitrary dosage of 140 to 150 mg. weekly. Cases include carcinomas of the breast, ovary, Fallopian tube, uterine corpus and cervix. A preliminary report of five cases in detail including carcinomas of the uterine corpus and cervix is presented. These patients have been receiving treatment for ten months. A theoretical consideration of the basis for this clinical investigation is given and our observations noted. Symptomatically, these patients have been definitely improved. Feeling of well-being, improved morale, control of menopausal symptoms, and increased libido have all been regularly observed and these observations alone seemed to us to warrant the administration of male hormone in this unfortunate group of patients. To date, there is nothing to indicate any regression or even retardation of the malignant process.

### Conclusions

1. All our patients have shown striking improvement in morale with feeling of well-being bordering at times on euphoria.

2. There has been a definite improvement of menopausal symptoms such as nervousness, insomnia, headache, depression, and, in most cases, hot flashes.

3. Increased libido has been consistent and marked.

4. With our arbitrary dosage (140 to 150 mg. per week) masculinizing symptoms have appeared in all patients and have included hypertrophy of the clitoris, development of a beard, and voice change. Acne-form eruptions have occurred in three of our original five patients and in many of subsequent cases.

5. Vaginal smears have tended toward the atrophic state and have changed little during treatment. In one patient some suggestion of cornification was seen from the beginning.

6. To date, there is nothing to indicate any regression or even retardation of the malignant process in manner comparable to the effect obtained in estrogenic treatment of prostatic carcinomas. In one of our original patients and in two subsequent cases, metastatic lesions have been seen to progress during the course of treatment (one carcinoma of cervix and two carcinomas of breast).\*

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\*Work is being continued.



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### Discussion

DR. ARTHUR H. CURTIS.—I have used, and have been greatly impressed with the therapeutic activity of the male sex hormone, testosterone propionate, since it first became available for use, some years ago. Please note that I say "therapeutic activity" rather than "therapeutic value," for the latter expression must still be held in abeyance.

We have long known that Perandren (Ciba), Oreton (Schering) or the same product manufactured by other houses, is potent in control of menstrual bleeding. Its dependability is limited to that menstrual period during which it is administered, but any product which suffices for temporary control of hemorrhage is a valuable aid in furthering permanent relief. Again, the male hormone eases the menstrual molimen, and now that the hormone is available in the form of orally administered tablets, it is a medicament of real value in selected cases.

The usefulness of testosterone propionate in the relief of angina pectoris has been verified by many observers. Here, its value is probably ascribable to the production of prolonged vasodilatation. In older men, in selected cases and with carefully adjusted dosage, the sense of well-being obtained, the disappearance of fatigue, the resurgence of youthful vigor and the return of youthful emotions are worthy of more than passing note.

I have become almost converted to the belief that estrogens, even in therapeutically modest dosage, are a definite menace to many women because of their carcinogenic influence. I avoid estrogens not only in those cases in which they cause bleeding, but also in all cases with extensive endometriosis, or adenomyosis of the rectovaginal septum, and in all those who have been operated on or irradiated for carcinoma. In these cases, the male hormone finds its field of greatest promise.

For relief of patients with refractory menopausal symptoms small amounts of testosterone propionate may be used in conjunction with estrogens, or independently. Strangely enough, although other symptoms are thereby commonly alleviated, the flashes tend to persist; in fact they may be made worse, even by modest oral dosage.

My experience with the male hormone in cancer cases, limited entirely to oral administration, parallels that of Dr. Abel. Contrary to the usual story in patients with malignancy, euphoria is a dominant feature. My patients have not had hypertrophy of the clitoris, nor have they been annoyed by inordinate sexual appetite. Hypertrichosis, however, has been more marked than in those younger women to whom we formerly administered somewhat less perandren parenterally for relief of menorrhagia. I assume that the considerably older age of cancer patients and the continuous administration of the hormone are factors. Regarding the effect on the cancerous growths it would appear at this premature time that the male hormone is an excellent palliative remedy, perhaps comparable with the helpfulness of palliative irradiation. Several cases in which I would have expected an early return of the growth have remained in a state of clinical arrest for a surprising period of time. When once the growth begins to recur, the hormone appears to be unavailing in arresting its progress.

DR. PHILIP F. SCHNEIDER.—This preliminary report on androgen therapy in malignancy of the female genitalia is of considerable interest regardless of the fact that no regression of tumor growth has been observed. The clinical improvement which has been reported in each patient, particularly in view of the advanced stage of the carcinoma, seems to justify the use of these substances and provides a method for further study of the relationship of the endocrines and carcinoma.

The conflicting reports in the literature regarding the results obtained with endocrine substances can usually be explained to some extent by the dosages employed. In the use of insulin, for example, the importance of accurate dosage is clearly demonstrated not only clinically but by means of blood sugar determinations. It is known that the nearest approach to the true physiologic normal can be obtained only by exact controlled dosage, while the administration of excessive or deficient amounts of insulin always produces abnormal physiologic effect.

In a considerable experience with estrogenic substances in the treatment of menstrual and obstetrical disorders due to estrogenic deficiency and in treatment of the menopause, similar observations have been made. The same symptoms and effects which are due to an estrogenic deficiency can be produced in the same patient by the administration of excessive amounts of estrogenic substance, while the nearest approach to the normal physiologic condition, both subjectively and objectively, can be obtained only by administration of the exact amounts necessary to compensate for the individual deficiency. This point is also demonstrated by our experience with the synthetic estrogenic preparation, stilbestrol. In our early experience with this substance the nausea, vomiting and bleeding accompanying its use were first attributed to a toxic effect of the substance itself. Subsequent experience has revealed that these so-called toxic effects were merely the results of overdosage. It seems logical to conclude that similar abnormal reactions may occur in the use of androgenic substances as is evident in all of the cases reported. The masculinizing effects and the occurrence of excessive libido which have been encountered in each of the five cases must be considered abnormal physiologic effects due to overdosage. It seems likely that with individualized dosage, which in this instance could be described as the maximum dosage possible in each instance, which would fall just short of producing the abnormal physiologic effects described could be expected to produce the maximum beneficial effect as far as tumor growth is concerned if any such beneficial effect is possible. The authors have made no statements as to the effect of androgenic therapy on bleeding which was present in any of the five cases when androgenic therapy was instituted. It would be interesting to know what their experience has been.

DR. EDWARD ALLEN.—Some months ago we began to look for suitable cases for this type of therapy. We felt in the beginning if any tumor were to be affected by androgenic therapy it should be an ovarian tumor. While waiting for such

cases to appear, we obtained four cases of carcinoma of the cervix. Rather large doses over a considerable period of time gave the same general effect as Dr. Abel described, but no effect on the symptomatology or changes in growth.

We then found three ovarian carcinomas that seemed to us to be in the right age group and with such extensive involvement that we could evaluate the relief of symptoms. One was a young woman of 27, one was 38 and one was 51 years of age. We taught these patients to take their hypodermics of perandren.

One case was so extensive that we felt justified in withholding any other type of therapy, while the other two were given x-ray therapy. The one receiving no x-ray is now dead of a generalized carcinomatosis. She had had a bowel obstruction for which she was operated upon twice. At the pulmonary operation, carcinoma was found spread all over the abdomen, but she had no visible growths at the time of the second operation. All three patients developed hirsutism but none showed appreciable changes in the clitoris. We did not question these patients specifically about their libido, but the two married ones did speak voluntarily of a marked increase. None of them gave evidence of or complained of menopausal symptoms.

One of the patients treated also by x-ray had undergone two operations, the first being done for the removal of one ovary only, no carcinoma being present or at least no diagnosis being made at that time. The second operation completed the castration and removed the uterus, x-ray therapy being subsequently given. When we first saw her, this patient had marked edema of the legs but at the end of a month and a half on androgenic therapy, this edema had all disappeared. She felt very much better and she is back at work. The last time I saw her she had what you might call euphoria, and, though she has hard nodular masses all over the left side of the abdominal wall, she appears to be a healthy woman.

The last case had been sent to Chicago to a general surgeon for excision of a tumor of the navel which had been treated by applications of silver nitrate by a physician who had not been aware that she had this huge tumor in the pelvis. The ovaries were removed but the uterus left in on account of its fixation in the pelvis by carcinoma. She gained fifteen pounds after the operation although she had masses of microscopic carcinoma that I believed would kill her in a short time. That is a year and a half ago and she is now getting discouraged with no longer any feeling of well-being. The androgenic therapy did not stop the growth of the tumor, but I do feel that all three of these patients lived longer than under ordinary circumstances and felt better during this time.

DR. ARTHUR H. CURTIS.—Two of the few cases that I followed had the following: one a primary growth which originated either in the tube or in the ovary, and the other, an extensive malignant granulosa cell tumor of the ovary. This is rather interesting in view of Dr. Allen's comments. Both of those are getting along very nicely.

DR. ABEL (closing).—I would like to amplify a little our report on the question of bleeding. Our original five patients had had either x-ray or radium, so that the menopause had been previously induced, and none had bleeding at the time of treatment. There were two cases of carcinoma of the breast, however, which were having menses at the time treatment was instituted. Menstrual periods stopped promptly in each case.

Relative to voice change, there is one other point of interest. In two of our original five patients, the vocal cords were edematous and pale on laryngoscopic examination. That was about the only change observed.

## DEVELOPMENT AND DEGENERATION OF OVUM AND FOLLICLE AS OBSERVED BY INTRAVITAL STAINING\*

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**A** CORRECT understanding of any organ is based upon the study of its anatomy and the study of its physiology. The anatomic approach consists of macroscopic and microscopic findings obtained after the death of the organ. The physiologic approach consists of animal experiments and chemical reactions during life.

The anatomic, especially histologic, approach has the advantage of providing readable pictures which stand before us as facts. It has the disadvantage that such illustrations demonstrate the structure, not the function.

The physiologic approach has the advantage of dealing with living tissue. It has the disadvantage that its findings are open to divergent interpretation.

Both methods are limited insofar as the ovary is concerned. Further progress is attained by combining both methods.

An example of such combination which proved to be of practical value is the use of endometrial biopsy as a mirror of ovarian function.

Another combination is the use of vital staining instead of postmortem staining. Dyes known by their physical and chemical properties, injected during lifetime, provide histologic pictures which tell us how organisms or individual tissues deal with or respond to these substances. Such method, therefore, throws light on certain unsolved problems.

As far as the ovary is concerned, the use of vital staining has been limited and not very successful. The reason is that these organs are as well protected chemically as they are physically.

It has been our endeavor to observe the development and degeneration of follicle and ovum under the influence of intravital staining, and to have seen whether or not new information could be obtained in regard to any of the numerous problems hitherto unsolved.

### Definition of Vital Staining

"Vital staining" can be defined as the injection of dyes into the living organism and the resultant staining of living tissues. "Supravital staining" is the term used when the tissues are removed first from the living organism and immediately stained afterward. The term "Supravital staining" should also be used when the stain is injected during life,

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but causes the death of the organism. "Intravital staining" is the method which is applied during lifetime, without causing death or lasting damage to the organism.

We shall see later that by microscopic examination, we can easily differentiate between intravital and supravital stained tissues and cells.

Dyes for vital staining can be injected intravenously, intramuscularly, intraperitoneally, subcutaneously, etc.

### History of Vital Staining

The history of vital staining covers a period of about seventy years. There have been two distinct phases.

The first phase consists of the injection of dyes and the observation of how they were eliminated by the organism. Thus, the functions of kidneys, liver, salivary glands etc., were studied (Heidenhain,<sup>1</sup> Krause<sup>2</sup>).

The second phase is interested in the storage of dyes within the organism (Aschoff,<sup>3</sup> Moellendorff<sup>4</sup> and co-workers). It has been found that the reticulo-endothelial system plays a leading role in this process.

Acid dyes are less toxic because they invade primarily connective tissue. Alkaline dyes are more toxic because they have no selective affinity and invade almost any type of tissue. Some dyes stain by diffusion (true staining), others are stored as granules. Those which stain by diffusion are eliminated rapidly. Those which are found as granules are stored over a longer period. The storage takes place in the cytoplasm. The living nucleus never takes any stain.

Parenchymatous and epithelial cells do not take any stain. Exceptions are those organs which eliminate the dye. The material which is injected into the blood stream is first deposited in the least important parts of the body, the connective tissue. From here it is transferred to the kidneys, salivary glands, intestines and liver for elimination.

The most important organs of the organism, the central nervous system and the reproductive glands, are best protected against invasion and therefore, hard to attack by vital staining.

### History of Vital Staining of the Ovary

Vital staining of the ovaries has been undertaken almost exclusively with dyes which are stored as granules. Borell,<sup>5</sup> a co-worker of Aschoff, observed the storage of lithium carmine in the granulosa of degenerating follicles. Goldmann<sup>6</sup> observed the presence of dye granules also in the granulosa of growing follicles. Eisler,<sup>7</sup> a co-worker of von Moellendorff, reported the occurrence of trypan blue in growing as well as degenerating follicles. Italian authors succeeded in staining the connective tissue of the ovary.

To force staining compounds into the ovum itself within the living ovary has not been achieved as far as we could ascertain from the litera-

ture. It has been our endeavor to fill this gap. The ovum is the very center of the reproductive female organs. To accomplish this seemed to promise broadening of our knowledge in various directions.

### Method and Material

Success or failure of our experiments depends upon the choice of the dye and the choice of the animal. So far as the stain is concerned, the following conditions have had to be fulfilled:

1. The dye has to be acid, water-soluble and not fat-soluble. Alkaline and fat-soluble compounds are toxic.
2. The dye has to have the property of fast diffusion, in order to invade tissues otherwise not approachable.
3. Dyes with the tendency to be stored as granules could be more or less discarded, since their almost exclusive use in the hands of experienced workers has not achieved the vital staining of the ovum proper.

Indigo carmine fulfills the conditions afore-mentioned. We used a 2 per cent solution. In a few instances, trypan blue and neutral red were used.

So far as the animal is concerned, the following conditions have had to be fulfilled:

1. The animal has to have sufficient size to permit intravenous infusion of the stain by the drip method.
2. The animal has to have sufficient power of resistance to withstand a general anesthesia over a long period, and then a laparotomy.
3. The animal has to have ovaries of satisfactory size and a sufficient number of active, i.e., growing and degenerating follicles.

The common house cat fulfills the conditions outlined. We used twelve 1- to 2-year-old females and one male. Ten cats received 2 per cent indigo carmine in increasing doses from 50 c.c. to 600 c.c. intravenously. Best results were obtained with the 200 c.c. dosage (intravital group). Larger amounts caused circulatory damage and death (supravital group).

One cat received 150 c.c. of 0.5 per cent trypan blue, 1 cat 90 c.c. of neutral red. The male cat was used to give us an opportunity to study the male sex glands by the use of vital staining. One cat was pregnant and gave us an opportunity to study the uterus, placenta, fetus, and the amniotic fluid.

Indigo carmine and trypan blue gave similar results so far as the ovary was concerned. We would like to point out, however, that the elimination of these compounds through the kidneys takes place in opposite ways.

Indigo carmine is eliminated through the tubules (Fig. 1), while the glomeruli show no stain. Trypan blue is eliminated through the glomeruli (Fig. 2), while the tubules are entirely inactive. The elimination of trypan blue is considerably slower than that of indigo carmine. The latter diffuses more rapidly into the tissues. Both principles were helpful in our work.

Neutral red is toxic because it invades all tissues. For our experiments, it proved to be of no value. In all instances of intravital staining, it was impressive to see the entire animal turn blue and still act normally after regaining consciousness from the anesthesia.

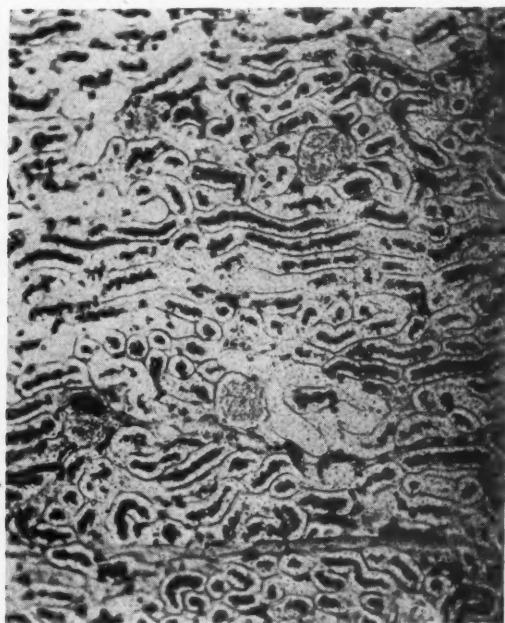


Fig. 1.—Kidney intravitaly stained with indigo carmine. The dye is in the tubules only. No dye in the glomeruli.

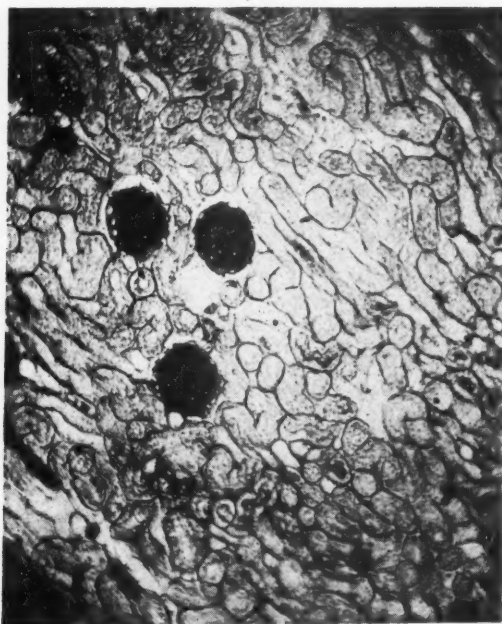


Fig. 2.—Kidney intravitaly stained with trypan blue. The dye is in the glomeruli only. No dye in the tubules.

The ovaries, tubes and uteri were removed at laparotomy. We also studied all other inner organs in some of the animals. We limit this report to the observations on the ovaries.

The removed organs were rapidly dehydrated, fixed and finally embedded in such a way, that any loss or diffusion of the intravitaly applied stain was avoided. Serial sections were made from all ovaries. Every other section was counterstained by different methods. The odd numbered sections received no counterstain and showed the vital stain only.

(Exact details of material and technique are published elsewhere.<sup>8</sup>)

### Observations on Ovum and Follicles

A picture of an intravitaly stained ovary under low power shows the albuginea to be blue but the primordial follicles colorless. The growing follicle is partly blue, partly without stain. High power gives us more detailed information.

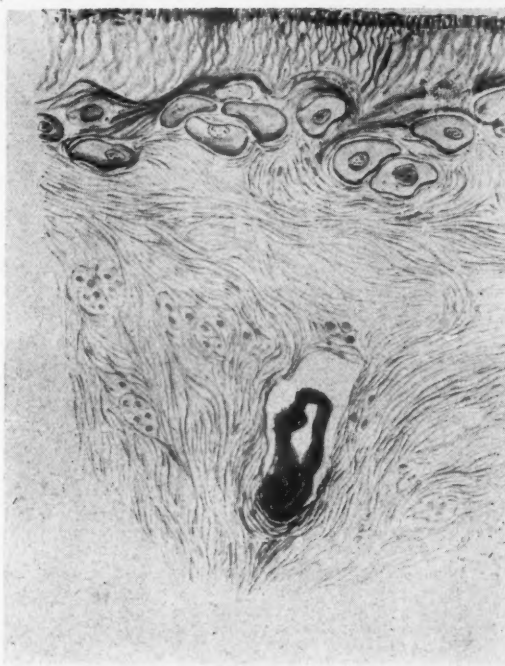


Fig. 3.—Ovarian cortex intravitaly stained. Primordial follicles near albuginea without stain. Collapsed, degenerated follicle in stroma stained.

Figs. 3 to 12 are black and white reproductions from colored slides. The dark areas represent the blue vital stain as described in the paper and observed in the original microscopic sections.

### Primordial Follicles

Under high power, we see the cardinal difference between primordial follicles in the resting stage and those which are degenerated (Fig. 3). Living primordial follicles do not take any vital stain. Degenerated primordial follicles are deeply stained. In other words, living primordial follicles, representing the most valuable building material of the ovary, are exceptionally well protected and at the same time excluded from



the circulation of blood and lymph stream. Degenerated follicles, on the other hand, are useless and therefore, the ideal place to deposit harmful foreign material such as the stains. They take the stain, even if the surrounding stroma remain untinged. They can also be recognized by the collapsed outline of the ovum.

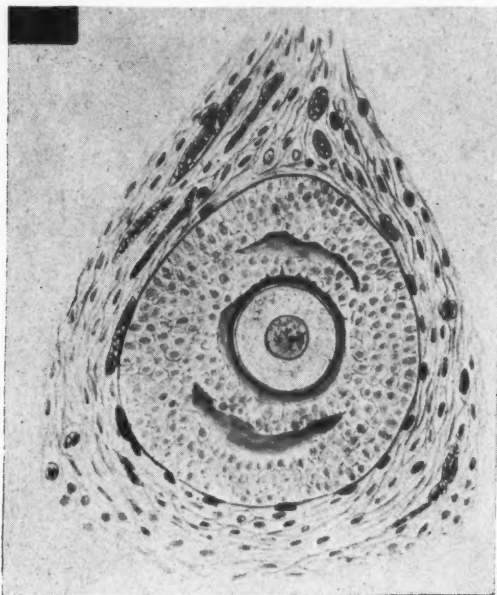


Fig. 4.—Small Graafian follicle intravitaly stained. The dye is found in the zona pellucida of the ovum and in the liquor folliculi.

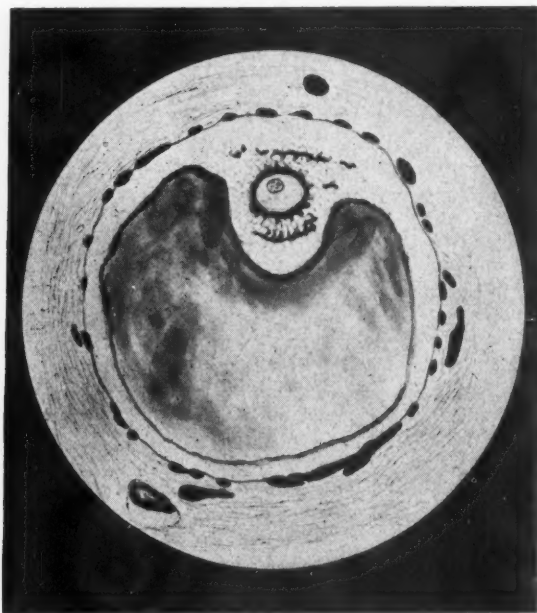


Fig. 5.—Large Graafian follicle intravitaly stained. Dye is present in zona pellucida, liquor folliculi and surrounding blood vessels.

### The Growing Follicle

The growing or Graafian follicle responds in a very typical way to intravital staining. We always find the material at two places, in the liquor and at the zona pellucida of the ovum. The inside of the ovum

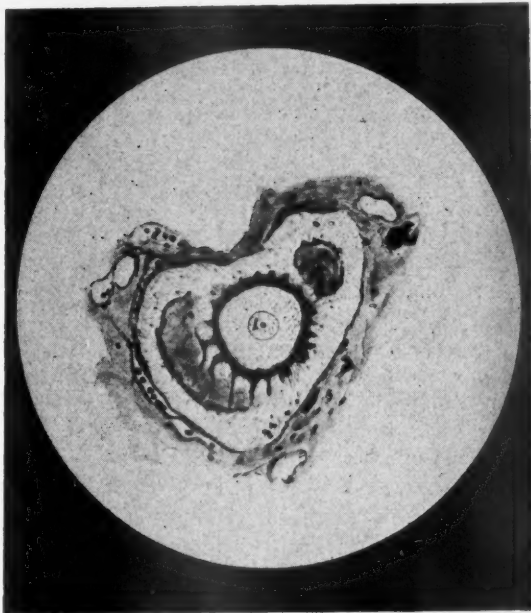


Fig. 6.—Supravitaly stained small Graafian follicle. Intensified staining of zona pellucida, liquor and blood vessels. Appearance of dye in nucleus of ovum.

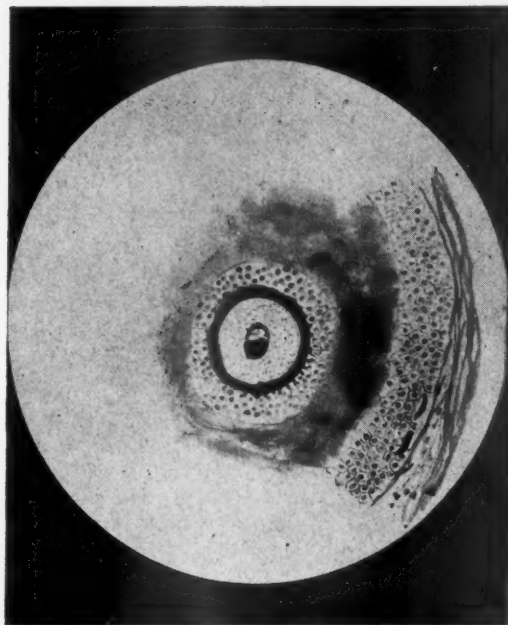


Fig. 7.—Supravitaly stained ovum of large Graafian follicle. Dye in nucleus and zona pellucida.

and the granulosa cells remains colorless. Fig. 4 demonstrates these facts in a small Graafian follicle. Here the liquor formation is just beginning in both poles. This follicle, by the way, shows also the theca interna cone which we described in previous publications. Fig. 5 represents a large Graafian follicle. Here, again, the zona pellucida surrounding the ovum is deeply stained. There is also considerable staining of the liquor especially in the neighborhood of the cumulus ovigerus, indicating that this part of the follicle is the center of circulatory supply. There is one degenerated primordial follicle deeply stained in the adjacent stroma.

By increasing the amount of dye to the point of the animal's death (supravital staining), we obtain the same features only more intensified. (Fig. 6.) The zona pellucida shows a blue double contour. The intercellular spaces between ovum and liquor in the corona radiata become visible. In addition, crystallized indigo carmine is present in the blood vessels, which is a sure sign of circulatory failure or death of the animal.

Fig. 7 demonstrates the ovum of a large Graafian follicle by supravital stain. The nucleus has taken up the stain, indicating the death of the ovum proper. The nucleus in the living ovum under intravital staining remains colorless. The ovum is the most sensitive cell in the follicle and the first one to die. The granulosa cells in Fig. 7 are still alive as indicated by their lack of blue stain.

Death is a slow process. Vital staining is a good method to study the progress of dying in the individual elements of the Graafian follicle. There is an important difference in the picture we obtain in ovaries when the animal dies and the Graafian follicles die with it on the one hand, and when the follicle degenerates in a living animal on the other hand.

### Degenerating Ova and Follicles

The degeneration of a follicle begins in the ovum. Vital staining is a method to detect the onset of degeneration at a time when no change of form or structure is visible.

Fig. 8 represents a small growing follicle with beginning degeneration. The ovum is flooded with blue material. The nucleus is darkest. The granulosa cells are stainless, therefore, still alive. There is no zona pellucida in the ovum of small follicles.

When degeneration progresses in small follicles, the ovum loses its round form and collapses. The granulosa cells disappear by absorption (Fig. 9).

An important fact is revealed by these pictures. The ovum governs the follicle. Degeneration of the follicle begins in the center or nucleus of the ovum, progresses to the ooplasm and finally leads to the destruction of the granulosa.

The degeneration of large follicles takes place in a similar way. The only difference is caused by the zona pellucida, which prevents the flooding of the entire ovum at one time. Infusion of the stain takes place where the zona is already weakened. Where the double contour indicates that the zona is still intact, we find the adjacent ooplasm unstained. (Fig. 10.)

As afore-mentioned, the degeneration of the granulosa cells does not coincide with or precede that of the ovum. It is the ovum which causes the degeneration of the granulosa cells. In larger follicles, this process begins at the inner layers adjacent to the liquor (Fig. 11.)



Fig. 8.—Beginning degeneration in small follicle, intravitaly stained. Entire ovum, nucleus and ooplasm flooded with dye.

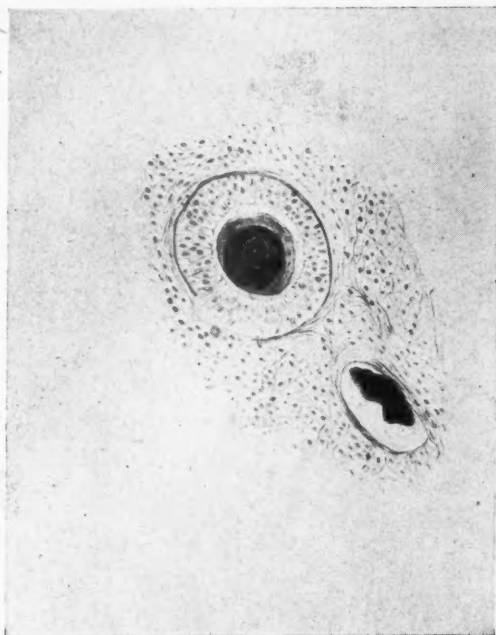


Fig. 9.—Progressing degeneration of two small follicles. Ovum flooded with intravital dye. Granulosa in one follicle absorbed.





Fig. 10.—Large follicle in degeneration. Ovum partly filled with stain. Nucleus stained.

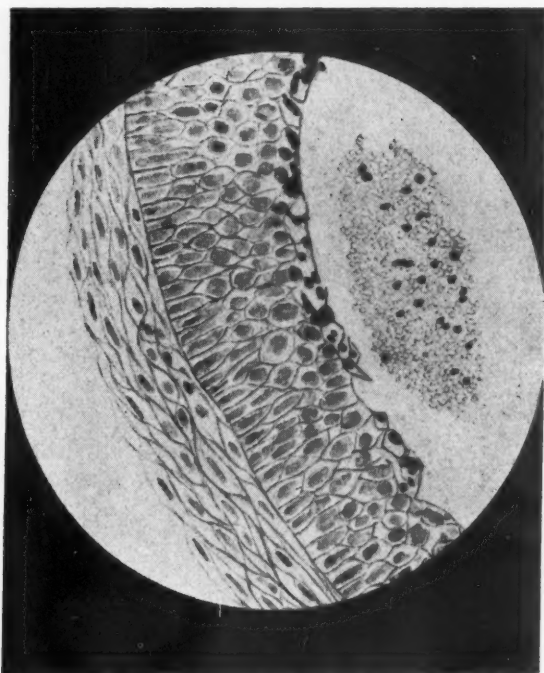


Fig. 11.—Large follicle. Beginning degeneration of granulosa. Dye present in inner layers and in chromatin droplets in liquor from broken-down granulosa cells.

The innermost layers of granulosa cells take up the stain, while the outer layers are still without color.

Finally, the outer layers also succumb. There is a difference in various parts of the follicular wall. The sectors close to the ovarian surface degenerate earlier than those located deeper in the ovarian stroma.

The liquor of degenerating follicles contains deeply stained chromatin derived from broken down and dissolved granulosa cells.

There are two distinct forms of follicle degeneration, the regressive and the progressive form.

We have seen here several pictures of the regressive form, which ends with the complete disappearance of the granulosa cells leaving nothing but a cyst without any epithelium.

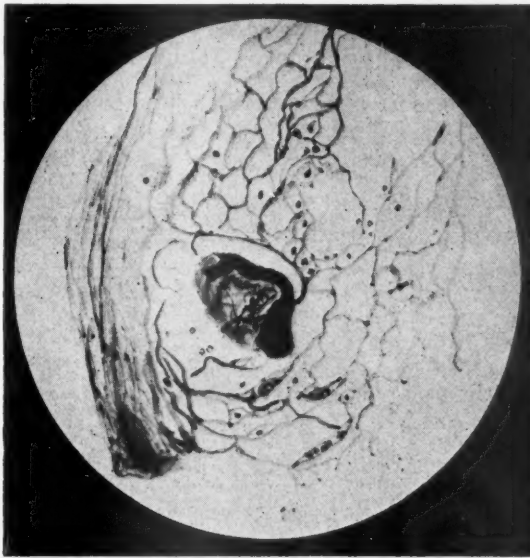


Fig. 12.—Degenerated follicle intravitaly stained. Pseudocorpus luteum. Collapsed ovum deeply stained enclosed in granulosa lutein cells.

The progressive form consists of a transformation of the granulosa cells into lutein cells, which become big by fat accumulation. These cells which fill out the entire follicular cavity do not take any of our stain on account of their fat content. (Fig. 12.) Such a degenerated follicle is not easily distinguished from a true corpus luteum. Only the presence of a degenerated ovum indicates that the follicle did not rupture. The ovum being dead is deeply stained and its shape in its final stages is one of complete collapse, an empty shell.

### Summary

Intravenous injection of indigo carmine and trypan blue is established as a method for intravital staining of the ovary. Not only the follicle walls, but also the ovum could be visualized. We observed the entire cycle through which most follicles go from the resting stage of the primordial follicle through the stage of the growing Graafian follicle into the various forms of degeneration. We have seen the different,

distinct, and typical ways by which the various forms and elements of ovum and follicle respond to the visible foreign material.

### Problems and Conclusions

1. *The Predominant Role of the Ovum.*—Intact ova and granulosa cells do not take the stain. It is a sign of cellular death or degeneration, if the dye appears within the nucleus or the cytoplasm. Intravital staining indicates the beginning degeneration of the ovum at a time when no change of structure is visible. This enabled us to show that the degeneration of any follicle begins in the nucleus of the ovum, progressing further to the ooplasm, and finally to the granulosa cells. In other words, the ovum governs growth and decay of the entire follicle. The findings verify the opinion of Robert Meyer<sup>9</sup> that the follicle depends upon the ovum in every phase of its development.

2. *The Origin of the Zona Pellucida.*—The zona pellucida of intact ova takes intravital stain. This fact can be used in the discussion concerning the origin of the zona. Early authors (Waldeyer,<sup>10</sup> Pflueger,<sup>11</sup> Nagel<sup>12</sup>) claim that the zona is a product of the granulosa cells surrounding the ovum. French authors contend that the zona is produced by the ovum itself. A third group believes that the inner layer of the zona is secreted by the ovum, the outer by the granulosa cells. Our observations show the intimate connection between the zona and the interspaces between the granulosa cells. No connection between the ovum proper and the zona could be visualized. This makes it probable that the zona is deposited from the outside to the ovum, like the calcium deposits of a hen's egg, and not secreted from the inside of the ovum.

3. *The Origin of the Liquor Folliculi.*—The origin of the liquor has been attributed to liquefaction or dissolution of granulosa cells. Some authors believe that the liquor is secreted by the granulosa cells. Our technique of vital staining indicates life or death of any cell. We have not seen one single instance of a degenerating dissolving granulosa cell in a living follicle. We have not observed any secretory activity of the granulosa cell. We have, on the other hand, demonstrated that the liquor depends closely upon the activities of the circulation of blood and lymph. It can, therefore, be concluded that the liquor is a secretory product derived from the blood vessels and the lymphatics, possibly modified by the influence of the granulosa cells, but definitely not by their liquefaction.

### Practical Problems for the Future

A great variety of physiologic and pathologic changes takes place in the ovary during lifetime. In addition, it is exposed to the influence of chemical, physical and electrical factors from the outer world. Medicine, itself, applies methods of treatment in all specialties, which may have some unknown effect upon the ovaries, especially the follicles and ova, in other words, upon the future generation. Two examples to be

named here are the possible effect of radiation and that of an overdosage of estrogens. What amount of damage is done to the germinative cells in these and other instances is of great importance.

Intravital staining as described previously is a method which gives us actual pictures of development and degeneration in the living ovary. It is a test for health, decay and death of any individual ovum and follicle.

It offers itself as a method to study the ovary, also after it has been subjected to any factor which may be pathogenetic. Animals could be treated first by radiation, various drugs, diets, etc., and then their ovaries studied after the dye has been injected intravenously. A wide field of experiments can be visualized in which intravital staining serves as a key which may open the gates to future knowledge and experience.

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## PAPILLARY LESIONS OF THE CERVIX UTERI IN PREGNANCY

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THE association of proliferative or papillomatous lesions of the cervix with pregnancy presents a problem in etiology and diagnosis which is not generally appreciated. In the literature these have been termed proliferative lesions, papillomas and condylomas.

Cullen<sup>1</sup> states that condylomas may occur during pregnancy and may be mistaken for squamous cell carcinoma.

Norris<sup>2</sup> in 1913, mentioned that condylomas of the cervix may occur during pregnancy. It was his belief that they were secondary to gonorrheal cervicitis. He recommended histologic examination to exclude carcinoma in such lesions, especially if they presented a cauliflower appearance.

Wharton<sup>3</sup> in 1921, considered condylomas of the cervix to be "one of the rarest of gynecological disorders." He reported three cases. Two were gonorrheal in origin, and one was tuberculous.

Hofbauer<sup>4</sup> in 1933, called attention to proliferative changes in the cervical mucosa and glands during the various stages of pregnancy. These were characterized by hyperplasia of the columnar epithelium, increased mitotic activity, vacuolization of many of the epithelial cells and occasional cell nests in the tissue beneath the mucosa. Squamous metaplasia of the cervical glands and hyperplasia of the epithelium of the squamous portion of the cervix were mentioned. In one of his patients, a small area of proliferation persisted for forty weeks after the termination of pregnancy. Hofbauer believed that the anterior pituitary hormone might be responsible for these growths. He also raised the question of the possibility of such epithelium becoming malignant. In his studies, he found no evidence of epithelial invasion as the cells always rested upon a definite basement membrane. He did not mention any gross changes.

Englander<sup>5</sup> in 1935, reported seven cases of polyps of the cervix in pregnancy. Though no microscopic examination was done, it was evident from his description that these should be considered in the category of papillary tumors of the cervix occurring during pregnancy. The age of his patients ranged from 19 to 26 years, six were operated upon, and in five excellent results were obtained. Abortion occurred in one, following operation. He described the lesions as both single and multiple growths.

More recently, Mershon<sup>6</sup> reported two instances of papillomas of the cervix occurring in young women, each aged 22, and in the sixth week of their pregnancies. These were at first diagnosed as squamous cell carcinoma, Grade I, by the pathologist. Additional biopsies and review

of slides by several pathologists resulted in the diagnosis being changed to papilloma in each instance. Both patients were treated with 2,300 milligram hours of radium, which resulted in the prompt disappearance of the tumors. Later biopsies disclosed no evidence of tumor.

DeLee<sup>7</sup> in his textbook states that he had seen three instances of nodular hypertrophy of the cervix in pregnancy. No further description is given.

We are reporting five cases of clinically evident lesions of the cervix occurring during pregnancy, and one case in which the diagnosis of pregnancy was only presumptive. Our first case has previously been reported by Mershon.

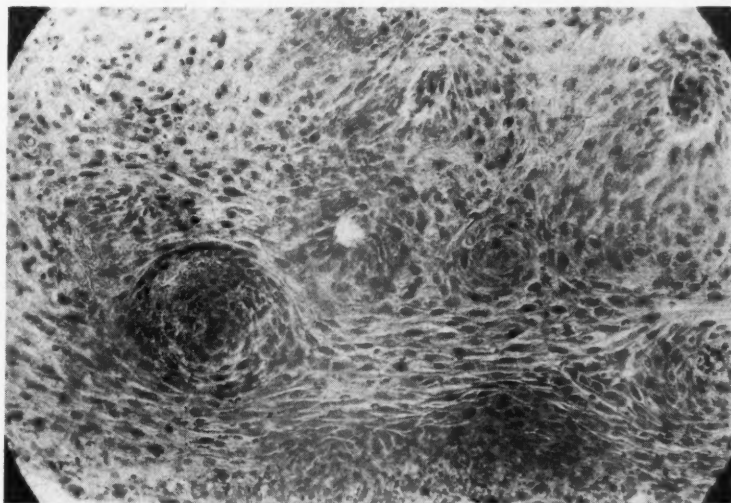


Fig. 1.—Multiple small confluent papillary stalks covered with hyperplastic epithelium. (×100.)

### Case Reports

**CASE 1.**—F. S., a white married female of 22 years of age, para ii, gravida iv, entered the Los Angeles County Hospital December 15, 1937, with a history of having had cramps and passage of clots on December 10, which was followed by the passage of an embryo. Her last menstrual period had been November 7, 1937. On physical examination, the cervix was observed to have bilateral lacerations and a polypoid circumoral growth. A biopsy was done at the time of dilatation and curettage on December 18, 1937. At this time the uterus was enlarged to one and one-half times normal size. The urine contained an occasional leucocyte and the blood Wassermann was negative. The first diagnosis was carcinoma and the patient was given 2,300 milligram hours of radium between December 27, 1937, and January 3, 1938. Another biopsy was done January 18, which showed no evidence of malignancy. The patient menstruated in February, 1938. When she was last seen in the clinic, on October 9, 1939, there was no tumor present. The cervix was smooth and apparently normal.

Histologic examination of tissue taken on December 18, 1937: A rectangular portion of cervix is composed of cervical glands and thick hyperplastic squamous epithelium. In the latter, there are two types

of changes. The first of these is characterized by a uniformly hyperplastic epithelium with broad, deep, rete cones and long, narrow papillae. (Fig. 5, Case III.) Some papillae appear to have arisen as small buds from the tunica propria and are seen only in the basal portions of the epithelium.

In the second type of change, the epithelium is much thicker. Its architecture in general is that of multiple papillary stalks covered with thick layers of epithelium which fuses indiscriminately with that of other stalks. (Fig. 1.) The papillary stalks do not have a visible tree-like arrangement, but contain multiple small blood vessels and a delicate stroma. The basal epithelium covering the stalks is tall and basophilic. Proceeding outward from the basal layer, the cells mature toward the periphery of each papillary unit much as do cells of the normal squamous epithelium of the cervix. Certain differences, however, can be noted. Throughout the epithelium the nuclei are larger than normal, vary in size to a moderate degree, are hyperchromatic and mitoses are more abundant than normal in the basal portion. Cell borders are fairly distinct and most of the epithelial cells are of the prickle cell variety. In the superficial cells near the surface, a few vacuolated cells are present. Keratinization may be seen in some of the surface cells.



Fig. 2.—Drawing of papillary tumors of the cervix ( $1\frac{1}{2}\times$  actual size).

The cervical glands are lined with a single layer of tall, columnar epithelium. Some contain areas of squamous metaplasia. A few of the glands are cystic. Throughout the tissue, there is abundant infiltration with neutrophils. In addition, there are a few areas of round-cell infiltration between the glands.

Small nests of epithelial cells in the connective tissue beneath the basement membrane are occasionally noted. They seem always to rest on a definite basement membrane. These may represent in some instances, complete plugging of the mouths of cervical glands.

CASE 2.—B. A. K. A white married primiparous female of 22 years of age was referred to the hospital for treatment of carcinoma of the



Fig. 3.—Large papillary stalk with multiple side branches. ( $\times 30$ .)

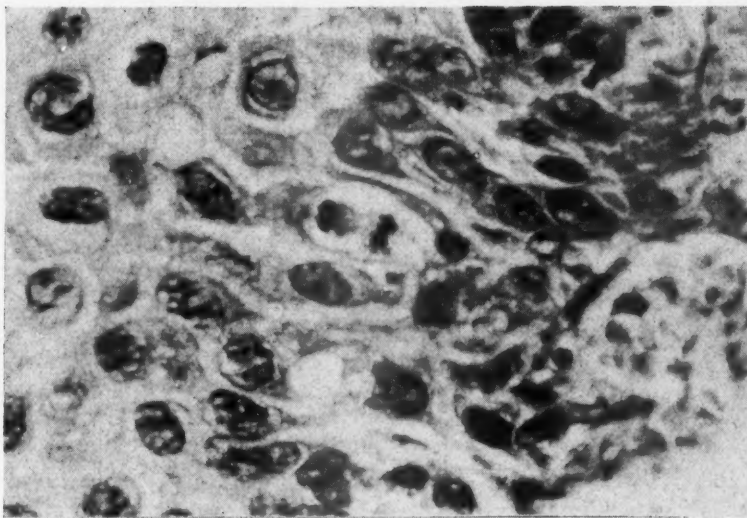


Fig. 4.—Large hyperchromatic nuclei and mitotic figure. ( $\times 450$ .)



cervix, Grade III. She entered February 7, 1940, nine days post partum, following delivery of a full-term baby at another hospital. Delivery had been aided by insertion of a bag to control hemorrhage. Patient stated she had had some white discharge since onset of menstruation at the age of thirteen. On examination, large papillary tumors of the cervix were noted. (Fig. 2.) The blood Wassermann was negative. On February 19, the cervix was given 800 milligrams radium (filtered through 1 mm. platinum). The appearance of the cervix began to improve promptly after treatment, but it was not entirely free of change until May 7, 1940. Beginning March 16, 1940, menstrual periods have been regular.

Histologic examination of tissue removed on February 19: This illustrates a third type of change in epithelial overgrowth. There are multiple, large, discrete, papillary growths of various sizes (up to 5 mm. in diameter). They have a central connective tissue stalk, in which there are many blood vessels and an occasional cervical gland. (Fig. 3.) From the large central stalk, branching papillary processes extend into thick squamous epithelium, and finally, near the surface, the smaller papillary stalks end in an arrangement similar to the second type described above. In the superficial portions of the tumors vacuolated cells are common. Mitoses are numerous. (Fig. 4.)



Fig. 5.—Broad deep rete cones and long narrow papillae. ( $\times 25$ .)

CASE 3.—J. E. C. A white married primiparous female of 18 entered the hospital August 16, 1940, in labor and at term. A low forceps delivery was done after six hours of labor. At time of delivery, a gray-white ulcerated lesion of the squamous portion of the cervix was noted. It extended throughout most of the circumference of the cervix near the external os. A biopsy was done at this time.

The blood Wassermann was negative. The urine was without change. The patient returned for examination four weeks post partum, on September 12, 1940, at which time only a thin, white scar could be seen on the cervix. Further periodic examinations were done and a cauteriza-

tion of the affected area on the cervix was performed on October 31, 1940. Cervix was pronounced completely healed on June 19, 1941.

Histologic examination of tissue taken at time of delivery: The section contains both cervical glands and thick masses of hyperplastic squamous epithelium. The changes differ little from those seen in Case 1. Acute inflammatory changes are rife. The broad, deep rete cones and long papillae are especially noticeable. (Fig. 5.) There is some squamous metaplasia of the cervical glands. (Fig. 6.)



Fig. 6.—Squamous metaplasia of cervical glands. ( $\times 150$ .)

CASE 4.—R. L. A white married primiparous female of 22 years of age, first entered the hospital on August 9, 1941, because of sudden pain in left upper quadrant, localizing in the right lower quadrant. There was moderate tenderness and guarding of the abdomen. The patient was operated on and several necrotic hydatids of Morgagni were removed. An early intrauterine pregnancy was observed. Recovery was uneventful. The patient next entered the hospital on October 7, 1941, for the removal of a condylomatous growth on the cervix, diagnosed in the outpatient department. She had complained of excessive vaginal discharge. The blood Wassermann and Kahn tests were negative. Cervical smears and complement fixation tests were both negative for gonorrhea. On examination, three large cauliflower growths, 2 to 3 cm. in length were seen on the cervix. These were removed by dividing them at their base and cauterizing the bleeding points. The patient delivered a full-term, 7-pound baby on April 15, 1942, at which time no mention was made of the cervix.

Histologic examination of tissue taken on October 7, 1941: There are large masses of hyperplastic epithelium in which a few cervical glands are present. Much of the growth has taken the form of large discrete papillary stalks, similar to that seen in Case 2. Areas of early keratinization are present; some of these form small "pearls." Vacuolization of the epithelial cells is common (Fig. 7).

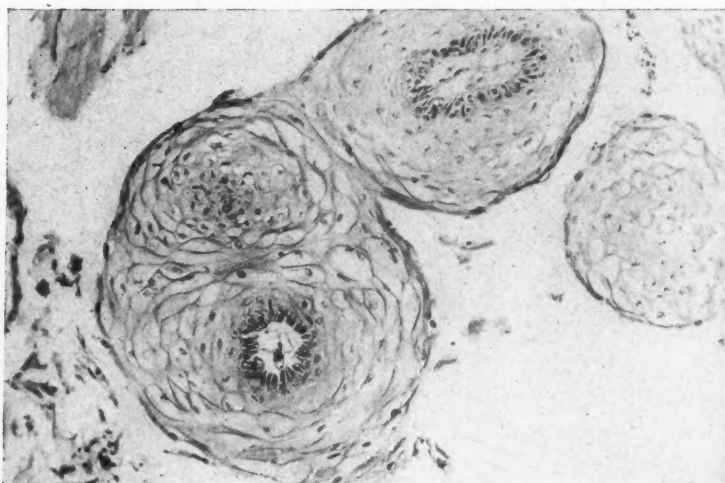


Fig. 7.—Vacuolization of epithelial cells covering papillary stalks. ( $\times 100$ .)

CASE 5.—M. M. A 17-year-old white married female came to the hospital on September 22, 1941, complaining of painful breasts and vaginal bleeding of four days' duration. This has followed a period of amenorrhea, which began following a menstrual period on July 1, 1941. On examination, the cervix was soft and the corpus was slightly enlarged. Blood Wassermann and Kahn tests were negative. The urine contained many pus cells. Dilatation and curettage was done on September 29, 1941. This showed no evidence of pregnancy. Her second entry to the hospital was on December 4, 1941. Again, she was considered a possible pregnancy because of a missed period in October. Cramps and vaginal bleeding had been present for twelve hours. A biopsy was taken of the cervix because of a small papilloma. Histologically, this is similar in all respects to Case 1. Mitoses were particularly abundant (Fig. 8). The patient returned several times to the clinic and, when last seen on April 20, 1943, the lesions had disappeared except for a small cervical erosion. She still complained of a vaginal discharge. Repeated cervical smears were negative for gonococcus.

This is a case of presumptive pregnancy only, but it is included because of the resemblance of the tumor growth to the others, and it presented much the same clinical problem.

CASE 6.—L. C. A. A primiparous Mexican female of 17 years of age, entered the hospital on February 12, 1942, at term and in labor. She delivered spontaneously a 7-pound, 2-ounce male infant. When a repair of cervical lacerations was done following delivery, a small pearl-white area of thickening was seen on the cervix. A portion was removed for histologic examination. So far the patient has not returned to the obstetric clinic.

Histologic examination: There is a small nubbin of epithelium projecting above the cervical mucosa. (Fig. 9.) Its architecture is that of the second-type lesions, i.e., thickening of the squamous epithelium with multiple small, papillary stalks.

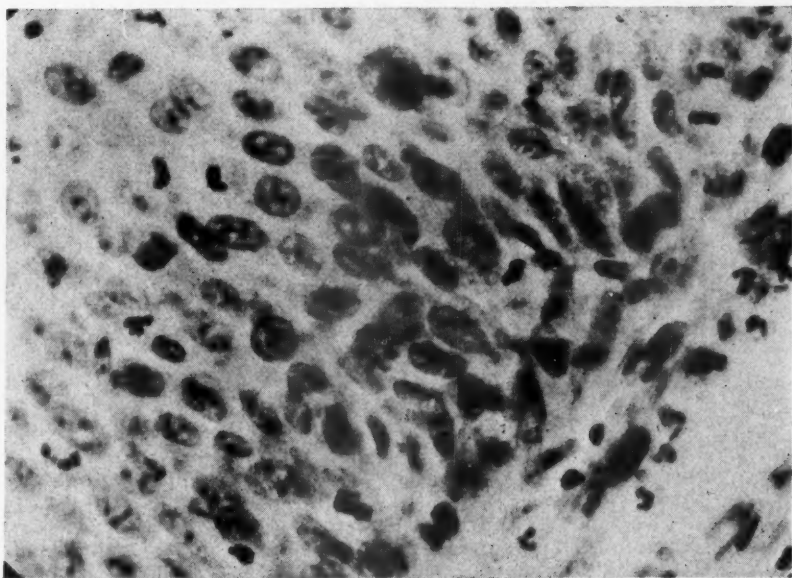


Fig. 8.—Many mitoses, hyperchromatic nuclei and variation in size of nuclei are suggestive of cancer. ( $\times 450$ .)

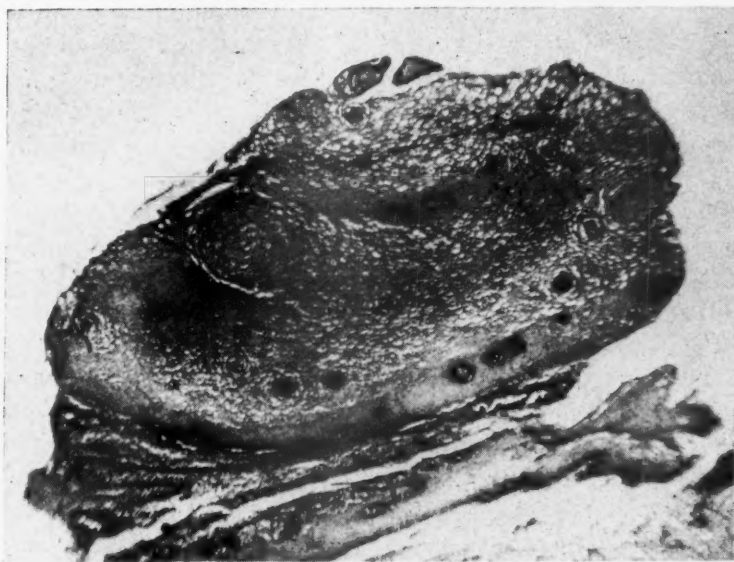


Fig. 9.—Small solitary papillomatous lesion. ( $\times 20$ .)

#### Comment

The changes seen in the cervixes studied may be conveniently divided into three groups. Type 1 and 2 lesions are practically always seen together, although in Case 5 (M.M.), one specimen shows only Type 1 change, but as a rule this type is noted only at the margins of the lesions.



The histologic changes characteristic of Type 1 are simple hyperplasia of the squamous epithelium with the formation of large, rete cones between which there are long, narrow papillae. Epithelial mitoses are more frequent than normal.

The macroscopic appearance of a cervix with Type 2 change is that of irregular nodular areas of gray-white or pearly thickening. Although the clinicians interpreted these as being on the portio vaginalis, cervical glands were always present which indicated that the tumor originated in the proximity of the external os. Microscopically, these differ from Type 1 in that the masses of epithelium are two to three times as thick, and the cells are arranged around papillary stalks.

In Type 3 change, there were gross papillary growths, or condylomas, some of which were 2 to 3 cm. in length. They arose in the same areas, near or at the external os. They had large central stalks, with a multitude of papillary side branches covered with thick squamous epithelium similar to that seen in other types.

Vacuolization of the cytoplasm of the cells, especially in the older, more superficial portions of the tumor, and evidence of acute inflammation both in the papillomatous growth and the adjacent cervical tissue, were present in all of the types of change observed. In addition, squamous metaplasia of the glands of the endocervix and proliferative changes in the columnar epithelium of the cervical glands, as described by Hofbauer, were seen in three of the tumors.

One of the noticeable histologic features of these tumor-like lesions is the rather large number of mitotic figures among the epithelial cells. This fact seems important as it suggests the possibility of carcinoma and somewhat complicates the pathologist's problem in reaching a diagnostic decision. In an effort to determine the significance of the fairly numerous mitotic figures, careful estimates of their numbers were made in the sections from the cases here reported. These counts were compared with the findings in similar biopsy sections from two other groups of patients, as indicated in Table I. The second group comprised young women who were pregnant or had had recent abortions, but who were without evident cervical lesions. The third group were young women who had not had recent pregnancies, and whose cervical tissues were apparently normal.

The obvious inferences to be derived from the data in Table I seem to be that the rate of mitosis in the stratified squamous epithelium of the normal cervix tends to be less than that of the pregnant uterus, while in the papillary lesions of the cervix in pregnancy the rate is still higher.

The significance of these data may be lessened by the small number of cases observed and by the wide variations in the mitotic counts in each group; however, they are presented for what they are worth.

One of the factors possibly concerned in the variations in the counts within the groups is that of natural rhythmicity of mitosis in animal

TABLE I. MITOSIS COEFFICIENT\*

1. Papillary lesions of pregnancy 6 cases—ages 17 to 23 years	0.8 to 4.8	Average 2.12
2. Pregnancy or abortion 8 cases—ages 16 to 36 years	0.0 to 3.2	Average 0.93
3. Nonpregnant. Normal cervix 6 cases—ages 23-43 years	0.0 to 0.32	Average 0.14

\*Mitosis coefficient—number of mitotic figures per 1,000 tissue cells. See Broders and Dublin: Rhythmicity of Mitosis in the Epidermis of Human Beings, *Proc. Mayo Clinic* 14: 423, 1939.

tissues. Recent studies which have been reported, are based upon observations of tissues of young animals, the foreskins of human infants one week old, and upon certain malignant tumors. These observations are, on the whole, of limited volume, but lead to the following tentative conclusions:

1. Normally growing tissues exhibit a definite diurnal rhythm of mitosis, the maximum intensity averaging from 2 to 4 times the minimum.
2. The rhythm differs as to time and intensity in different kinds of animals, and in different organs in the same animals.
3. Malignant tumors fail to exhibit any recognizable rhythm. In other words, the mitotic activity is independent of the rhythm of normal body tissues; that is, cancerous tissue growth is uniformly constant, without diurnal periodicity.

It may well be that the variations shown in our groups were in part related to natural diurnal periodicities. Other possible influences might be assumed such as a rhythmicity associated with the menstrual cycle. So far as we are aware, no observations intended to determine such variations have been reported.

It must be recognized that chronic inflammatory lesions of non-pregnant cervixes present certain microscopic features similar to those which have been described in these papillary lesions of pregnancy. But, it is our observation that in such inflammatory lesions we do not find (1) an equal degree of mitotic activity, (2) hyperchromatism and inequality of nuclei of similar grade, (3) frank papillomatous changes of sufficient size and complexity to be recognized as condylomatous.

Condylomas of the cervix occurring in the absence of pregnancy are indeed rare. At the Los Angeles County Hospital our records are not complete, but in our experience, we have seen it only once.

It is evident that these growths are not malignant in that they are not invasive. The question arises as to whether they may be a pre-malignant lesion and some time after pregnancy may become invasive. However, carcinomas of the cervix reported during pregnancy occur for the most part in an older age group, i.e., 30 to 40. Nowhere in the literature were we able to find that such benign papillary lesions had been described as antecedent to carcinoma. The possibility remains, however, that they may become malignant.

The etiology of these papillary growths is not known. Hofbauer believed that the anterior pituitary hormone may be responsible for proliferative changes in the cervical glands. Certain experimental work, however, indicates the importance of estrogen as a cause of proliferative changes in the vagina and cervix. Overholser and Allen<sup>8</sup> produced atypical growths in the epithelium of the cervix of the monkey by the use of prolonged injections of ovarian hormone combined with trauma. These were not autonomous growths as they disappeared with cessation of hormone administration. V. Suntzeff<sup>9</sup> et al. produced carcinoma-like growths in the vagina and cervix of mice with the injection of large doses of estrogen. In experiments with hybrid mice, Allen and Gardner<sup>10</sup> produced squamous cell cancer of the cervix by the long-continued use of estrogen (16.6 mg. to 50 mg. of estradiol benzoate per week) in animals which survived the treatment for more than one year. Crossen and Loeb<sup>11</sup> produced similar lesions in mice which had passed the reproductive period by the same means.

Another likely etiological factor is infection. Because of vaginal discharge, two of our patients were suspected of having gonorrhea but this was not proved by smear or complement fixation test. Nonspecific chronic cervicitis, with discharge of irritating secretions might provoke such a growth. The microscopic evidence of diffuse acute inflammation of both the hyperplastic tissue and the underlying cervix gives credence to this theory.

The ages of the patients, 22, 22, 18, 22, 17 and 17, with an average of 19.6 years, is probably significant. The ages of these patients are similar to those reported by Englander and Mershon.

In summation, one might postulate that in young pregnant women in whom perhaps the tissues of the body have not yet completely finished their growth cycle, the action of the hormones associated with pregnancy, particularly estrogenic hormone, combined with infection of the cervix may give rise to papillary overgrowth of the squamous epithelium at or near the external os.

That these lesions should be recognized as benign and not treated as cancer is a lesson to be remembered by clinician and pathologist alike. This cannot be overemphasized. The pathologist must give careful attention to the clinical history as well as to the histologic criteria that differentiates these lesions from carcinoma. Only in this way can mistakes be avoided. In the last analysis, the following triad forms the basis of correct diagnosis and sound judgment in the treatment of these lesions: (a) Youth, (b) pregnancy, (c) lack of invasion of cervical tissue by the epithelial growths.

### Summary and Conclusions

1. Five instances of proliferative or papillary lesions of the cervix uteri associated with pregnancy are reported. One case of presumptive pregnancy is included.

2. The ages of the patients varied from 17 to 22 years. The average was 19.6 years.

3. The lesions were seen at various stages of pregnancy ranging from the second month to the time of delivery.

4. The proliferative growths were single or multiple, varied in size from small pearly gray-white areas to papillomas raised 2 to 3 cm. above the surface and were always located at or near the external cervical os. Usually they were described as being circumoral.

5. Microscopically, they were characterized by various grades of proliferative change in the squamous epithelium, i.e., (a) simple thickening of the epithelium; (b) greatly thickened irregular epithelial units indiscriminately fused together with confluent tiny papillary stalks; (c) large papillomatous growths.

6. Cellular changes such as irregularity in size of nuclei hyperchromatism, unusual mitotic activity and vacuolization of the cytoplasm may tend to confuse the diagnosis with carcinoma. True invasion, however, does not occur.

7. The etiology is not clear. Age, hormones and infection may all be responsible.

8. The treatment is conservative. Large, discrete tumors can be removed surgically. Radiation therapy is of value in treating extensive multiple lesions.

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## MANUAL REMOVAL OF THE PLACENTA

### A Policy of Treatment

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**R**ETENTION of the placenta following delivery has always been considered a major complication in obstetrics. The high maternal mortality associated with this complication justifies such an attitude.<sup>1, 2</sup> Death usually is caused by sepsis or by hemorrhage with its accompanying shock. In recent years, with the advent of effective therapeutic agents for combating infection and with the availability of large quantities of blood for immediate transfusions, the mortality rate associated with manual removal of the retained placenta has been steadily reduced.

Although in obstetric literature, considerable attention has been devoted to manual removal of placenta, we believe that certain aspects of this problem have not been emphasized sufficiently. The need of a general policy for routine treatment of this condition is desirable. We believe that the treatment is dependent upon the solution to two fundamental questions, namely:

1. If spontaneous expulsion of the placenta does not occur, how much time should elapse before a manual removal is indicated?

When spontaneous expulsion of the placenta has failed, one should be able to establish an optimal time for attempting manual removal in order to prevent serious effects from hemorrhage. Furthermore, one should expect a lower incidence of sepsis when the blood loss is kept at a minimum. This is in accordance with the practice of good obstetrics.

2. Is there evidence that placental retention is associated either with abnormal uterine function or with faulty implantation of the placenta?

The failure of spontaneous expulsion of the placenta usually is attributed to (1) "failure of separation," (2) separation with retention because of "hour-glass" constriction of the lower uterine segment, (3) the so-called "adherent placenta."

With the use of the active principle of ergot (ergonovine), given intravenously (when the infant's anterior shoulder is born), the physiology of normal placental separation must be revised. Apparently, separation occurs because of the immediate marked decrease in the size of the placental site. Certainly, there is no evidence that separation occurs by the classical formation of the retroplacental hematoma, because, in most instances, the separation is so rapid and complete that such a hematoma usually is not found. Although "failure of separation" of the placenta per se can occur, the incidence should be much lower with the use of intravenous ergotrate, because placental

separation is markedly enhanced by this drug. It may be argued that the routine use of ergotrate results in an increased incidence of "hour-glass" constriction of the lower uterine segment. This may be true. However, failure of expulsion of the placenta because of this "hour-glass" constriction is compensated by the increase in the number of placentas which separate. Hence, the necessity for manual removal should not be increased.

If, with the use of this oxytocic, "failure of separation" does not occur, one may assume that the failure of expulsion is a result of the "adherent placenta" caused by placenta accreta, rather than by poor uterine function. Placenta accreta is the coherence of the placenta to the myometrium, resulting from the absence of the decidua basalis, particularly of the stratum spongiosum. Such accretion may be produced by either direct contiguity to or invasion of the myometrium by the chorionic villi, or by myometrial incursion into the placenta septa. These changes may involve all or portions of the maternal surface of the placenta. Consequently, this involvement may be classified as complete, partial or focal. The complete type implicates all of the cotyledons of the placenta, the partial, one or several, and the focal, a portion of only one cotyledon.

*Incidence.*—Manual removal of a retained placenta following the delivery of a viable infant was performed 217 times at the Boston Lying-in Hospital from 1920 to 1943, inclusive. During that period, 45,602 patients were delivered of viable infants. Manual removal of the placenta was performed once in every 210 deliveries or 0.47 per cent. Twenty-nine (13.1 per cent) of the 217 patients were delivered in the home.

TABLE I. INDICATIONS FOR MANUAL REMOVAL

INDICATIONS	TOTAL CASES	PER CENT
Hemorrhage	116	53.4
Retention	101	46.6

*Indication for Manual Removal.*—The indications demonstrated in Table I have been divided into two groups, namely, hemorrhage per se, and retention with hemorrhage. During a period from 1920 to 1930, there were only forty cases of manual removal. A large percentage of these cases was occasioned by hemorrhage following delivery by accouchement forcé. During recent years, the chief indication has been retention.

*Duration of Pregnancy.*—The duration of pregnancy could be determined accurately in most cases. Approximately one-fourth of the cases (22.1 per cent) of manual removal occurred in patients who delivered prematurely, as shown in Table II. Three-fourths of the patients delivered at term. This study does not substantiate the general opinion that a large percentage of retained placentas is associated with premature labor.<sup>2</sup> The size of the infant at term appears to be an unimportant

TABLE II. DURATION OF PREGNANCY

PREGNANCY BY WEEKS	TOTAL CASES	PER CENT
28 to 34 weeks	17	7.8
34 to 38 weeks	31	14.3
38 to 42 weeks	163	75.2
Over 42 weeks	6	2.7

factor. The incidence of postmaturity is only 2.7 per cent, and, therefore, does not constitute a significant factor.

*Duration of Labor.*—The general opinion that prolonged labor increases the morbidity rate following manual removal is not confirmed by analysis of our series, as demonstrated in Table III. Schwartz and Richards<sup>3</sup> reported a morbidity rate of 71.4 per cent for patients who were in labor over thirty hours, and seven of them were febrile in the puerperium. The morbidity rate in this group was 30.4 per cent, which is only slightly higher than that of the large group of patients who were delivered within thirty hours (26.6 per cent) after the onset of labor. However, 10.6 per cent of the patients were in labor over thirty hours. This confirms the general impression that prolonged labor is a factor in placental retention.

TABLE III. MORBIDITY—RELATION TO LENGTH OF LABOR

HOURS OF LABOR	TOTAL CASES	MORBIDITY	
		NUMBER OF CASES	PER CENT
Under 10	101 (46.5%)	26	25.7
10 to 20	73 (33.7%)	25	34.2
20 to 30	20 (9.2%)	4	20.0
30 and over	23 (10.6%)	7	30.4

TABLE IV. MORBIDITY—RELATION TO TYPE OF DELIVERY

	NORMAL DELIVERIES		OPERATIVE DELIVERIES		MORBIDITY			
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	NORMAL DELIVERIES		OPERATIVE DELIVERIES	
					NUMBER CASES	PER CENT	NUMBER CASES	PER CENT
Primiparas (42.4%)	30	32.6	62	67.4	9	30.0	17	27.4
Multiparas (57.6%)	88	70.4	37	29.6	24	27.2	12	32.4

*Type of Delivery.*—Delivery effected either by normal or by operative procedures apparently does not alter the morbidity rate, as exhibited in Table IV. There is a slightly increased morbidity rate following manual removal of placentas in multiparas who were delivered by operative procedures.

*Maternal Morbidity.*—There were sixty-two morbid patients in this series, following manual removal, as demonstrated in Table V. Excluding two patients who died within twenty-four hours, the morbidity rate for 215 cases is 28.8 per cent. Excluding the ten patients who were febrile after subtotal hysterectomies, the corrected rate is 24.1 per cent. In this group of ten cases, placenta accreta was found in nine instances.

The remaining patient underwent a hysterectomy because the uterus was ruptured during the manual removal. This is the only instance of ruptured uterus in this series, but its very possibility definitely emphasizes the need of extreme gentleness on the part of the operator.

TABLE V. MATERNAL MORBIDITY AND MORTALITY RATES

TOTAL CASES	MORBIDITY		CORRECTED MORBIDITY		MATERNAL MORTALITY		
	TOTAL CASES	PER CENT	TOTAL CASES	PER CENT	NUMBER CASES	PER CENT	CORRECTED
217	62	28.8	52*	24.1	4	1.8	1.3%†

\*Excluding 10 patients who were febrile after hysterectomy.

†Excluding a patient who died from pneumococcic meningitis.

TABLE VI. MORBIDITY—RELATION TO BLOOD LOSS

AMOUNT IN C.C.	TOTAL CASES	MORBIDITY	
		NUMBER OF CASES	PER CENT
Under 500	129	27	20.9
500 to 1,000	66	24	36.3
Over 1,000	22	11	50.0

TABLE VII. MORBIDITY—TIME OF PLACENTAL RETENTION

HOURS RETAINED	TOTAL CASES	MORBIDITY		AVERAGE BLOOD LOSS C.C.
		NUMBER CASES	PER CENT	
Under 1 hour	77 (35.5%)	18	23.3	339
1 to 2	63 (29.0%)	13	20.6	406
2 to 3	27 (12.5%)	10	37.0	598
Over 3 hours	50 (23.0%)	21	42.0	544
Totals	217	62	28.8*	471

\*Excluding two patients who succumbed within twenty-four hours.

The important factors which appear to influence the morbidity rate are presented in Tables VI and VII. Table VI emphasizes the fact that the morbidity rate is markedly increased in proportion to the degree of blood loss. Table VII reveals an increase in the morbidity rate in relation to the elapsed time from delivery until the time of manual removal. The correlation between the blood loss and the elapsed time, together with their relationship to the morbidity rate, is impressive.

**Mortality.**—Four patients out of the 217 in this series died following manual removal of the placenta. The uncorrected maternal death rate is 1.8 per cent. Excluding the patient who died on the twelfth postpartum day from pneumococcic meningitis, the corrected mortality rate is 1.3 per cent.

The case histories of the four deaths are summarized as follows:

CASE 1.—(1928.) Mrs. B. is a 23-year-old para iii. She was three and one-half weeks overdue by dates. After five hours of labor, the patient was delivered normally of an infant weighing 9 pounds, 6¼ ounces. The placenta failed to separate within the allotted time, profuse bleeding



followed, and the patient went into shock. Two blood transfusions were given. One hour and forty minutes after delivery, a manual removal was attempted. Part of the placenta was removed in pieces. During this procedure, the uterus was inverted. The remainder of the placenta could not be removed; therefore, the uterus was replaced and a rapid supravaginal hysterectomy was done, without anesthesia. The patient succumbed to shock and hemorrhage five and one-half hours after delivery. Permission for autopsy could not be obtained. Microscopic examination of the placenta showed a partial placenta accreta.

CASE 2.—(1934.) Mrs. McK. is a 28-year-old, unregistered para vi. The patient had a precipitate delivery at home, which was followed by profuse vaginal bleeding because of retained secundines. She was admitted to the hospital one and one-half hours later in profound shock. Two blood transfusions were given, and a manual removal of the placenta was done. The patient was afebrile until the eleventh postpartum day. She then experienced a chill and the temperature rose to 104 degrees. She had a convulsion. The neck was found to be stiff. A lumbar puncture revealed the spinal fluid to be turbid with a cell count of 2,500. Stained smears showed gram-positive diplococci. In spite of serum therapy, the patient succumbed on the twelfth postpartum day. Autopsy findings showed a pneumococcal meningitis.

CASE 3.—(1936.) Mrs. R. is a 22-year-old primipara at term. After forty-seven and one-half hours of desultory labor, the patient was delivered of a 9 pounds, 1 ounce infant by low forceps. In spite of the use of pituitrin and several attempts at Credé and Gabeston-Monjon the placenta could not be delivered. Therefore, three hours after delivery a manual removal of the placenta was done. The atonic uterus was packed with gauze. A blood transfusion was given. The total blood loss was estimated to be 500 cubic centimeters. The patient became febrile, with a temperature of 106 degrees by the third postpartum day. An intrauterine culture grew anaerobic streptococci. Prontosil was given without any therapeutic response. During the course of the next twenty-three days, the patient continued to be febrile. Seven more blood transfusions were given. An x-ray of the chest showed evidence of pulmonary infarction. On the thirty-sixth postpartum day, the patient succumbed to bronchopneumonia. Permission for autopsy could not be obtained.

CASE 4.—(1939.) Mrs. McC. is a 33-year-old para iv, who was delivered of twins at home in the twenty-ninth week. The patient was transferred to the hospital several hours later because the placenta failed to separate. Seven and one-half hours after delivery, manual removal of the placenta was attempted. Part of the placenta was removed in pieces. The uterus was packed because of profuse hemorrhage. A supravaginal hysterectomy was done. In spite of six blood transfusions (3,600 c.c.), the patient succumbed within twenty-four hours. An autopsy was performed. Microscopic examination of the placenta showed multiple areas of focal accreta.

It is obvious that two of these patients succumbed to shock and hemorrhage because of forceful piecemeal removal of retained placentas which proved to be placenta accretas. The other two patients died from infection. It is difficult to believe that manual removal was the fatal factor

in causing the death of the patient who succumbed to pneumococcal meningitis. The patient who died of bronchopneumonia evidently had infected pulmonary emboli which probably originated from a thrombophlebitis of the pelvic veins. Undoubtedly, the infection was introduced at the time of the manual removal.

TABLE VIII. UTERINE TAMPONADE AFTER MANUAL REMOVAL

TOTAL CASES	AVERAGE BLOOD LOSS C.C.	TOTAL NUMBER OF TRANSFUSIONS	AVERAGE TRANSFUSION PER PATIENT	MORBIDITY	
				NUMBER OF CASES	PER CENT
18 (8.1%)	933	47	2.9 (1,467 c.c.)	10	55.5

*Uterine Tamponade.*—Eighteen patients (8.2 per cent) in this series had uterine tamponade. The morbidity rate is 55.5 per cent. Uterine atony was the indication for packing in twelve of these patients following successful manual removal of the placenta. The high morbidity was undoubtedly influenced by the severe blood loss which made uterine packing imperative. The remaining six patients had placenta accretas, four of whom underwent supravaginal hysterectomies. Excluding these four cases, the morbidity rate is 42.8 per cent. Sulfanilamide gauze packs were used in five patients. Two of the patients became febrile, establishing a morbidity rate of 40.0 per cent. This small series of sulfanilamide gauze packs does not merit a definite conclusion, but it is believed that the use of such packs will lower the morbidity rate. Uterine tamponade, if necessary, should be undertaken as a separate procedure with utmost regard for asepsis.

*Placenta Accreta.*—It is not the purpose of this paper to discuss the clinical entity of placenta accreta in detail. This obstetric complication has been thoroughly studied in a report by Irving and Hertig.<sup>4</sup> Those authors report an incidence of one case of placenta accreta in every 1,956 deliveries.

TABLE IX. RETAINED PLACENTAS DUE TO PLACENTA ACCRETA

TOTAL CASES	PARITY		AVERAGE BLOOD LOSS C.C.	TYPE OF ACCRETA			TREATMENT		OUTCOME OF PATIENT	
	PRIMIPARAS	MULTIPARAS		FOCAL	PARTIAL	COMPLETE	MANUAL REMOVAL	HYS-TERECTOMY	LIVED	DIED
24 (11.0%)	5 (21.0%)	19 (79.0%)	1,041	2	20	2	7	17	22	2 (8.3%)

In this series of 217 cases where manual removal of the placenta was attempted, some degree of placenta accreta was encountered twenty-four times. This represents an incidence of 11.0 per cent (Table IX) or once in every 1,900 deliveries. All of these cases of placenta accreta were

verified by careful microscopic study.<sup>5</sup> We would emphasize the increased degree of blood loss, morbidity and maternal mortality rates occurring in this group of patients.

*Oxytocic Drugs Following Delivery.*—The use of oxytocic drugs following the delivery of the infant did not appear to be a significant etiologic factor in retention of the placenta. Approximately one-half of the cases did not receive pituitrin or ergotrate after delivery of the infant. The incidence of retained placentas, in relation to total deliveries, was greater in the patients who were delivered at home, where oxytocic drugs were not used until after the expulsion of the placenta.

*Infant Deaths.*—Two hundred and twenty-three viable infants were delivered from the 217 patients in this series. This figure includes six sets of twins, or an incidence of one in every thirty-six patients (2.7 per cent). Six patients had hydramnios and were delivered of fetal monsters. These two groups (twins and hydramnios) appear to be somewhat significant, as they comprise 5.5 per cent of the cases. There were ten macerated stillborn infants, establishing an incidence of 4.9 per cent. The gross fetal mortality rate for the 217 cases is 11.2 per cent. Excluding the ten macerated infants, the rate is 7.0 per cent. Excluding three fetal monsters, the corrected fetal death rate is 5.7 per cent. We believe that macerated infants, twins, and hydramnios are etiologic factors worthy of consideration.

*Miscellaneous.*—The history of manual removal of the placenta in preceding pregnancies was not frequent. In this series, it was encountered only four times in three patients. There were surprisingly few patients who had previous abortions and curettements. One patient had been delivered in the preceding pregnancy by a classical cesarean section. Following a pelvic delivery, the retained placenta was found to be accreted in the region of the old section scar. Two patients had multiple uterine fibroids. Eleven patients had pregnancy toxemias.

Placental abnormalities, such as circumvallate, bipartite, and succenturiate lobes, were encountered in 5.0 per cent of the cases. Two patients had previous placenta previas, and two had previous toxic separation of normally implanted placentas.

*Transfusions.*—In this series of 217 patients, sixty-nine (31.7 per cent) were transfused. To these sixty-nine patients, 132 transfusions were given, an average of 1.9 transfusions per patient. Ninety-one transfusions, or 68.9 per cent of all the transfusions, were given to thirty-four patients who had either placenta accreta or uterine tamponade, making an average of 2.7 transfusions per patient for this group. It has been the policy of this clinic for the past fifteen years to have available donors conveniently at hand whenever a manual removal is performed.

Recently, a modified blood bank has been established. Group O Rh-negative and Group O Rh-positive blood are stored in adequate quanti-

ties. The blood is drawn into a flask containing 500 c.c. of a special preservative which enables us to store the blood for at least thirty days. The a and b factors of the serum are treated by Witebsky's inactivating substance, which obviates the necessity of cross-matching.

Routine blood grouping and Rh factor determination are done on all of our patients at the first prenatal visit. If the need arises, Rh-positive or Rh-negative blood can be given immediately, according to the Rh status of the patient. Emergency patients who require transfusions are always given Rh-negative blood until the Rh factor has been determined.

### Discussion and Treatment

It appears evident that the problems associated with the retained placenta are influenced by hemorrhage, sepsis, and faulty implantation of the placenta.

A morbidity rate of 20 to 25 per cent in the least complicated cases must, at least for the present, be accepted.\* This rate is markedly increased if the blood loss exceeds 500 c.c. per patient. In order to prevent such blood loss, it is imperative that the placenta should not be allowed to remain in the uterus longer than one to two hours. Certainly, nothing is gained by permitting the placenta to be retained for a longer period of time.

We believe that the term "failure of separation" should be retained. In these cases, a complete line of cleavage can readily be established. Failure of separation in this instance, obviously, results from poor uterine function. Since establishing the routine use of intravenous ergotrate, administered when the infant's anterior shoulder is born, we have not observed any increase in the number of retained placentas. If retention does occur, the causation is more likely a result of "hour-glass" constriction than of "failure of separation." Furthermore, even if expulsion does not occur after the use of this drug, we have been impressed by the small blood loss associated with placental retention.

Faulty implantation of the placenta (placenta accreta), popularly termed "adherent placenta," should be regarded as an important, not infrequent, and very serious cause for retention of the placenta. We are aware of the fact that the incidence of placenta accreta is exceptionally high in this series. We are not cognizant of such an incidence in any previously reported series of manual removal. A diagnosis of placenta accreta should be made, we believe, when a clear line of cleavage cannot be found between the placenta and uterus. In this series, when a cleavage plane was absent, all the placentas revealed some degree of accreta when examined microscopically. Furthermore, not a uterus was removed which did not show some evidence of accreta. Hence, we feel that the term "adherent placenta" is a misnomer.

\*This apparently irreducible morbidity rate should warrant consideration of the prophylactic administration of parenteral sulfadiazine or penicillin in all cases where manual removal is necessary. Unfortunately, the offending organism is the anaerobic streptococcus. We have found that the early use of Elliott treatments is most effective in this type of infection.



When the diagnosis of placenta accreta is made, irrespective of type, no further attempt should be made to remove the placenta pelvically, but an immediate supravaginal hysterectomy should be done. It could be argued that many of the patients with focal and partial accretas could be treated successfully by the vaginal route. That such a method of treatment is resorted to in most clinics must account for the absence of accretas in other papers on manual removal, compared with the high incidence encountered in this series. We feel that in some of the maternal deaths said to be caused from hemorrhage and shock which occurred in cases where difficulty was encountered in establishing a cleavage plane, the operators actually were dealing with patients who had focal or partial placenta accreta. The only two deaths in this series resulting from hemorrhage and shock were associated with such conditions. One patient had a partial accreta, while the other patient had multiple areas of focal attachments. When the affected portions were forcefully removed, severe hemorrhage resulted from the rupture of the coherent maternal sinusoids. Although uterine packing was immediately performed, both patients were in irreversible shock by the time hysterectomies could be performed. Heroic measures at blood replacement were of no avail, and both patients died. Such catastrophes should emphasize the immediate dangers which are present even when the degree of accreta is minimal. Conversely, there is undoubtedly less risk to the patient who has a complete placenta accreta, because the operator probably will be unable to dislodge the placenta, and, therefore, will perform an immediate hysterectomy. Moreover, we believe that many of the delayed hemorrhages in the puerperium and probably many of the cases with a "placental polyp" are the results of partial or focal placenta accreta which were unrecognized at the time of manual removal. A certain number of these patients will subsequently demand radical measures before the vaginal bleeding can be properly controlled.

These experiences have proved to us that a definite plan of treatment should be carried out in all cases of placental retention. Within one-half to one hour following delivery, a diagnosis of a retained placenta should be made. Preparations should ensue for immediate manual removal. We believe very strongly that this operation should be carried out in an operating room equipped for an immediate laparotomy, as well as for manual removal. After the patient is anesthetized, a Credé expression should always be tried. If this procedure fails, manual removal should immediately be attempted. Uterine packing should be resorted to if there is any question that the uterus is not contracting properly.

If a placenta accreta is encountered, the uterus should be packed at once with sulfanilamide gauze and an immediate supravaginal hysterectomy be performed. The pack is removed, vaginally, prior to amputation of the cervix. The amount of hemorrhage is markedly reduced by this method. Usually, ten grams of sulfanilamide powder is placed under the peritoneal flap covering the cervical stump. Multiple trans-

fusions are usually necessary when the blood loss has been great. In this manner, we believe we should be able to reduce further the mortality arising from shock and hemorrhage associated with either uterine atony or faulty implantation of the placenta in patients who demand manual removal.

### Conclusions

1. An analysis of 217 cases of manual removal of the retained placentas following the delivery of a viable infant is reported. This operation was necessary once in every 210 deliveries.

2. The gross mortality rate is 1.8 per cent, and when corrected, is 1.3 per cent.

3. The gross morbidity rate is 28.8 per cent, and when corrected, is 24.1 per cent.

4. The morbidity rate is markedly increased by the following factors (Table X):

- (a) A blood loss exceeding 500 cubic centimeters.
- (b) A placenta allowed to remain in the uterus more than two hours following delivery.
- (c) The necessity for uterine tamponade.
- (d) Associated placenta accreta.

TABLE X. SUMMARY OF FACTORS

FACTORS	TOTAL CASES	AVERAGE BLOOD LOSS, C.C.	MORBIDITY	
			NUMBER OF CASES	PER CENT
Blood loss over 500 c.c.	88	786	35	38.6
Placenta retained over 2 hours	76	608	31	40.7
Uterine tamponade	18	933	10	55.5
Placenta accreta	24	1041	14	58.3

5. Placenta accreta occurred in 11.0 per cent of all cases. We believe such cases are best treated by abdominal supravaginal hysterectomy, rather than by the pelvic route.

6. A policy of treatment in manual removal of the placenta is presented. We believe this policy will further reduce the number of deaths from shock and hemorrhage.

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## NONINVOLUTION OF THE PLACENTAL SITE

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THE extreme efficiency with which the postpartum uterus solves its own problems of hemostasis, of reduction in bulk, and of return to the nongravid state readied for subsequent reimpregnation, is noteworthy. The mucosal surface of the postpartum uterus is recovered within the first 14 days, and often at an even more rapid rate. The necrotic slough has been cast off by this time and the gland stubs have served as the hub from which the new epithelial covering springs. The bulk of the uterine muscle is reduced sharply either by loss of cytoplasm of the individual cells, or by actual loss of cells by autolysis, or by fatty degeneration.

Important in this process are the blood vessel changes, notably in the postpartum uterus. A physiologic obliteration takes place as the arteries undergo obliteration and hyaline degeneration, whereas the veins undergo thrombosis with subsequent organization. With increasing parity, there is increased elastic tissue around the blood vessels due largely to incomplete or imperfect absorption during the puerperium, as Shaw's<sup>1</sup> studies emphasize. Goodall<sup>2</sup> has found that new blood vessels are formed within the lumina of the old blood channels in subsequent pregnancies. Schwarz<sup>3</sup> has confirmed these views and adds that in the more marked grades of subinvolution, masses of incompletely absorbed, dead, swollen elastic tissue are found between the muscle bundles.

Williams<sup>4</sup> has found that the placental site is handled in such fashion as to leave a minimal scar upon the uterine mucosa. The placental site is exfoliated by a process of growth of the new endometrium from beneath the site, as well as by ingrowth from all sides. This requires six weeks or even longer in contrast to the more rapid rate of mucosal surfacing. This process apparently is designed to prevent scarring of the endometrium with each pregnancy—otherwise, increasing parity ultimately would ablate any further possible sites for implantation of the fertilized ovum. After six weeks, it is virtually impossible to detect microscopically the placental site.

Schwarz has described the microscopic picture of the subinvolved uterus as one with an increased amount of elastic tissue around the blood vessels and between the muscle bundles, together with the formation of new blood channels within the lumina of the degenerated and obliterated vessels. Clinically, this uterus, which is seen by the gynecologist more frequently than by the obstetrician, is one larger than normal. Its consistency is soft and boggy. Characteristically, its cut surface is made irregular by projections of thickened blood vessels. The pa-

tient's complaints are often those of bleeding, discharge, discomfort. Described with this is chronic endometritis associated with malpositions of the uterus or infections elsewhere in the pelvis.

Well known, too, is the entity of retention of bits of placental tissue and its clinical pattern of bleeding, failure of uterine involution often requiring operative intervention.

It is the purpose of this brief report to emphasize the fact that there may be failure of involution of the placental site itself without the associated picture of subinvolution as it has been described, or without the retention of placental tissue. This would represent failure of the physiologic process of obliteration of the large vessels underlying the placental site. Varying degrees of failure will be apparent in the attached case reports.

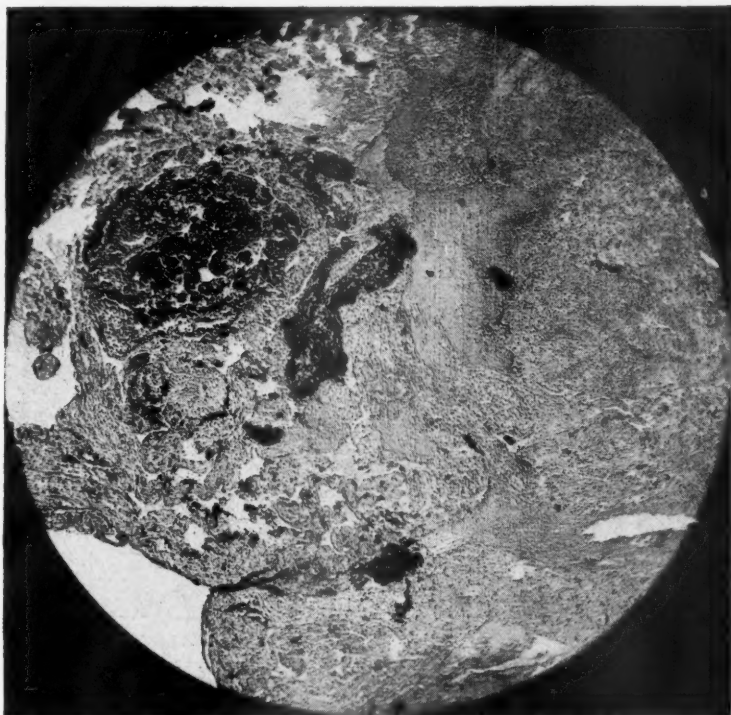


Fig. 1.—Case 1. Low-power view of placental site tissue with placental site giant cells, a hyalinized stroma which is infiltrated by chronic inflammatory cells and a few hemosiderin-laden macrophages. Vessels are but partially obliterated.

### Case Reports

Three cases will be presented from the Boston Lying-in Hospital. Each may be noted as a clinical variant of the picture of noninvolution of the placental site, but coming at different periods in the puerperium.

CASE 1.—Mrs. C. D. (B.L.I. 96262) is a 29-year-old para i, who was delivered without event as a breech. The uterus contracted well following delivery. The placenta and membranes were complete. Her postpartum course was uneventful with a physiologic amount of lochia.



On the tenth postpartum day, her uterus had involuted to twice normal size and she was discharged without complaint from the hospital on her twelfth postpartum day. From discharge onward, the patient continued to flow, using 2 to 3 pads daily, without cramps. On the day of entry, 6 weeks postpartum, she gushed suddenly and painlessly an estimated cupful of bright blood. She was not lactating.

On examination, the uterus was one and a half times normal size, the os would admit a finger. No other abnormalities were found. Upon both dull and sharp curettage, only a small amount of endometrium was obtained, the total measuring 1.5 by 1.5 centimeters. The patient stopped bleeding and her puerperium was completed with no more flow.

On microscopic examination, no placental tissue could be found. The endometrium was atypical secretory in nature. Placental site tissue was found with placental site giant cells and a few hemosiderin-laden macrophages. Vessels in this area were but partially obliterated. (Fig. 1.)

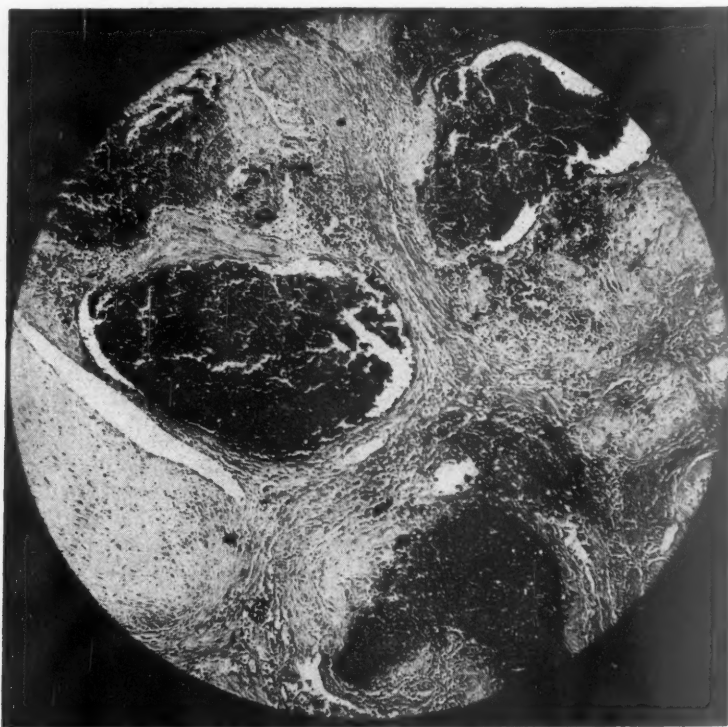


Fig. 2.—Case 2. Low-power view showing numerous patent blood vessels of the placental site. This demonstrates failure of the usual mechanism of thrombosis and organization or by endarteritic obliteration. There is intense subacute and chronic inflammatory cell infiltration, with some placental site giant cells. No villous structures are seen.

CASE 2.—Mrs. C. B. (B.L.I. 95791) is a 38-year-old para vii, whose previous pregnancies had been normal. The present pregnancy was complicated by a 10 cm. fibroid mass, which rose out of the pelvis early in pregnancy, but caused no further trouble. After an easy labor, the patient delivered normally and had an uneventful puerperium, flowing only the physiologic amount. The placenta and membranes were complete. On the day of discharge at 11 days postpartum, the uterus was

twice normal size, in good position, with the os closed. Two days later, on the thirteenth postpartum day, the patient began to bleed at home an estimated 5 to 6 pads, but this responded to oral ergotrate gr.  $\frac{1}{320}$  thrice daily. However, two days later, the patient again began to bleed despite the oral ergot preparation, and required hospital admission for blood loss which was estimated at 500 cubic centimeters. On admission, 15 days postpartum, the patient was in fair condition with a pulse of 90, a blood pressure of 136/80. The uterus was thrice normal size, the os was 2.5 cm. dilated. Curettage was performed using both dull and sharp curettes, obtaining a mass of tissue measuring 4 by 3 by 3 centimeters. The patient bled no more and her puerperium ran out a subsequent normal course.

On microscopic examination, first as a frozen section, numerous patent blood vessels of the placental site were found demonstrating failure of thrombosis and organization. Some were visible grossly. On permanent section, the curettings demonstrated hemorrhage and necrosis of the decidua, some of which contained enormously enlarged vessels (probably relatively enlarged by contrast with involution of the surrounding tissue), with improper and poor obliteration of their lumina by the endarteritic and thrombotic process. Some myometrium also was present which contained extremely large vessels and a few placental site giant cells. For the most part, the picture was one of intense subacute inflammation associated with subinvolution or noninvolution of the placental site. No villous structures were seen. (Fig. 2.)

CASE 3.—Mrs. M. H. (B.L.I. 94716) is a 29-year-old para viii. This pregnancy was complicated by intermittent bleeding throughout the middle trimester, which was found to have been due most likely to a placenta circumvallata found at delivery in the patient's home. The placenta and membranes were complete. Following the last of her previous 5 full-term pregnancies, the patient flowed for 8 weeks and had required curettage. No microscopic diagnosis could be obtained from that hospital. Following the present pregnancy, she began to flow the usual amount of lochia, but continued for the next 21 days, using 6 to 8 pads daily even though on bed rest and oral ergot preparations. At the end of this time, the patient was admitted to the hospital because of continued bleeding and weakness. The uterus on examination was twice normal size, the os admitted a fingertip. The patient was curetted with both dull and sharp curettes, obtaining a mass of tissue measuring 2 by 1.5 by 0.5 centimeters.

Microscopic examination revealed endometrium composed for the most part of orderly and regularly arranged glands in the early proliferative phase, showing nuclear pseudostratification with some mitotic activity. The supporting stromal cells were naked. In areas, there was considerable necrosis with a few cells of the decidual type apparent. There were numerous large vessels in the myometrium and in the supporting stroma which were thrombosed. Some of them, however, showed lumina which were not yet completely obliterated. There was minimal inflammatory cell infiltration. The myometrium was composed of regularly arranged bundles of smooth muscle cells. Some of the cells were quite swollen and still showed pregnancy changes. Placental site was still apparent.

After curettage, the patient continued to bleed using 4 to 8 pads daily. Bed rest and ergot therapy were still without effect. After continued observation for 8 days, with no cessation in bleeding, a supravaginal

hysterectomy was performed. Convalescence was smooth following operation.

On gross examination, the uterus measured 8 by 8 by 6 centimeters. Upon opening the uterus, there was found an adherent mass on the anterior uterine wall. This measured 5 by 2.5 by 1.5 cm., and was composed of partially organized blood clot and necrotic material difficult to identify.

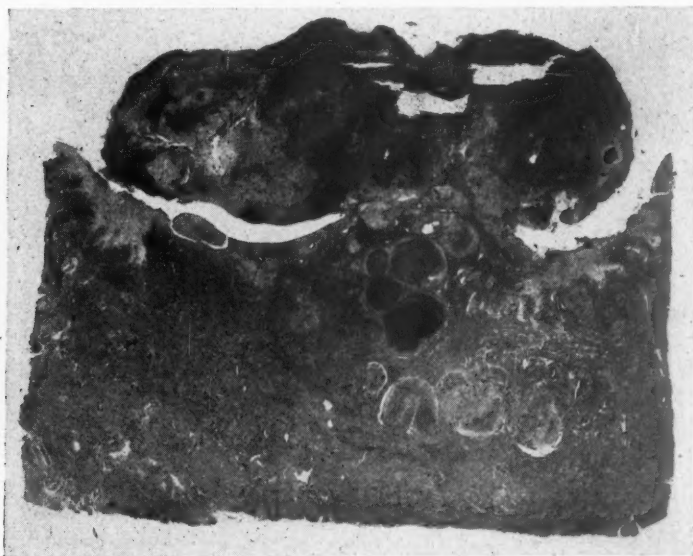


Fig. 3.—Case 3. Photograph of the microscopic slide in Case 3 demonstrating the adherent mass on the anterior wall. This represents noninvolved placental site intermingled with blood clot. The underlying vessels are incompletely obliterated, although a few are filled with organizing blood clot or hyalinized material. The superficial endometrial layer has grown to cover partially this polypoid mass, which is yet adherent to the uterine wall by only a very small pedicle. There are a few hyalinized or ghost villi left, suggesting some retained placental tissue.

On microscopic examination, the endometrium of the general uterine cavity was completely repaired, showing nuclear pseudostratification and some mitotic activity in the superficial layer. The supporting stromal cells were naked of cytoplasm. The adherent mass described grossly was found to be a noninvolved placental site with intermingled blood clot, and with a few hyalinized villous structures present as well. The underlying vessels, both the decidual sinusoids and the spiral arterioles, show varying degrees of thickening of the vessel walls, and some are obliterated by organizing thrombus or by hyalinized material. More vessels, however, are incompletely obliterated with erythrocytes still free within their lumina. The superficial endometrial layer has grown to cover partially this polypoid mass, which is yet adherent to the uterine wall by only a very small pedicle. (Fig. 3.) The picture is one of noninvolution of the placental site associated with a remnant of placental polyp.

Sections taken from the lower uterine segment showed no alteration in their normal architecture. The supporting myometrium was composed of regularly arranged bundles of smooth muscle cells. The serosal surface was intact. A few lower segment glands were present.

### Discussion

These cases were selected to demonstrate the varying clinical pictures possible during the early puerperium due to noninvolution of the placental site. The process of physiologic obliteration of the vessels of the gravid uterus is a generalized one, but it is most marked in the region of the placental site. It is in this area of placental attachment where one would suppose the maximal numbers of blood vessels would occur. Elsewhere in the uterus, the surface epithelium regenerates rapidly and the vessels are but a minor part of the picture. In the placental site, however, the whole area is extruded, as it were, along with the bulk of its obliterated vessels. This pinching off process requires an average of 6 weeks, as Williams has shown, and is completed by an undergrowth of endometrium from all sides, as well as from beneath the placental site. As a consequence of the magnitude of the process, the sequence of obliteration of vessels, slough and extrusion of the placental site takes not only longer, but if incomplete, carries a much greater bleeding potential than the simpler regression elsewhere in the uterus.

Generalized failure of involution prolonged beyond the normal limits has been described as subinvolution of the uterus. We are not dealing with that entity in these cases, for this problem is one in the early weeks following delivery. In these cases, the physiologic regression of muscle and vessels takes place properly in all spots but the placental site. In the third case presented (Fig. 3), the endometrial surfacing had covered even polypoid placental site, as well as endeavoring to undergrow it. This truly seems a localized failure rather than the generalized picture known as chronic subinvolution.

Neither is this the picture of placental polyp, although in the last of the three cases some hyalinized "ghost" villi were yet apparent within the mass of placental site tissue. The true placental polyp has viable tissue in addition to these "ghost" structures.

Certainly subclinical variations of this picture are seen—the case which clears up on ergot and bed rest at home after bleeding small amounts only for some period of time. This case does not require curettage. Case 1 illustrates that this problem can exist in the primipara, rather than to accept it as a function of multiparity. It would seem more likely to occur, however, in multipara because of the very nature of the process. In Case 3, the patient undoubtedly had noninvolution of the placental site with her last pregnancy, for this, too, had required curettage. With the present pregnancy, she developed a more severe degree of the same picture.

Curettage seems to be an easy, effective treatment. It would have been satisfactory in Case 3, had not the curette missed the small area of attachment of the placental site to the uterine wall.



### Summary and Conclusions

1. Three cases are presented in clinical and pathological detail to illustrate the entity of noninvolution of the placental site.

2. Such a problem is one belonging to the early weeks of the puerperium rather than existing as a chronic state of generalized incomplete uterine involution—"chronic subinvolution of the uterus."

3. There seems to be failure of complete physiologic obliteration of the placental site vessels so that hemorrhage accompanies the casting off of the placental site. This is in contradistinction to placental polyps. Chronic inflammation plays but little part in these cases.

4. Treatment consists of the usual ergot preparations and bed rest. Failing this, curettage should be curative.

5. It would seem that this is more likely to occur in multipara, and that there may well be a tendency for this problem to appear in subsequent pregnancies.

Dr. Frederick C. Irving is to be thanked for his criticism of the manuscript.

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## THE INFLUENCE OF STILBESTROL UPON LACTATION

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**S**TILBESTROL is being employed as an aid in suppressing lactation. During its administration, the infant is not placed at the breast. Since the treatment is employed in the absence of nipple stimulation, certain questions arise: (a) Is the suppression of lactation primarily the result of the medication, or (b) is it due to the withdrawal of the nipple stimulation?

Abarbanel and Goodfriend<sup>1</sup> and Karnaky<sup>2</sup> deny that stilbestrol will depress lactation in the presence of normal nursing.

Stewart and Pratt,<sup>3</sup> Diddle,<sup>4</sup> Davis<sup>5</sup> and Connally<sup>6</sup> reported that stilbestrol will inhibit lactation in spite of normal nursing.

Because of this difference of opinion in the literature, we wish to present certain results of our investigations.

### Material and Methods

This study is based on observations upon a series of 250 patients, who were delivered in the Hospital of the University of Pennsylvania between January, 1940 and January, 1942.

The effect of stilbestrol upon lactation was observed in 4 groups of patients under the following conditions:

- A. In absence of nursing; no pumping of breasts.
- B. In absence of nursing; with pumping of breasts.
- C. Following short period of nursing.
- D. During nursing.

In groups A and C, the effect of stilbestrol upon lactation was measured in terms of its influence upon breast discomfort, engorgement, leakage during treatment, and leakage after discontinuation of stilbestrol. In groups B and D, the effect of treatment was recorded as ounces of milk obtained by pumping, or grams of milk taken by the infant.

The nursing routine included nursing on alternate breasts for 20 minutes, every 4 hours. Breasts were supported properly, fluid intake was encouraged, and strenuous catharsis was omitted. Mothers were given specific instructions as to how to nurse properly, and how to keep the breasts clean and well supported.

The routine treatment for each group was as follows:

- 1. Fluid intake at least 3,000 c.c./24 hours.
- 2. No unusual cathartics.
- 3. Support of breasts—no tight binders.
- 4. Stilbestrol 1 mg., three times daily for 5 days.

#### *A. Treatment in Absence of Nursing—No Associated Pumping of Breasts.—*

Stilbestrol was given to 50 patients who did not nurse at any time,

and whose breasts were not pumped. Treatment was started within 48 hours of delivery, with the results shown in Table I.

TABLE I. TREATMENT IN ABSENCE OF NURSING—NO ASSOCIATED PUMPING OF BREASTS—50 PATIENTS

	PATIENTS
1. Breast discomfort	0
2. Engorgement	0
3. Leakage during treatment	0
4. Leakage after discontinuation of treatment	5
5. No symptoms	45
Total	50

*B. Treatment in Absence of Nursing—With Associated Pumping of Breasts.—*

Fifty patients did not nurse at all but were pumped at regular intervals beginning 48 hours after delivery. An electric breast pump was used at 4-hour intervals on alternate breasts. As soon as 8 ounces of milk were secured per 24 hours, stilbestrol treatment was begun and continued simultaneously with pumping for 5 days. The results are shown in Fig. 1. Note the drop in milk secretion within 24 hours of the start of stilbestrol administration, and the continuing decrease as long as the drug was administered.

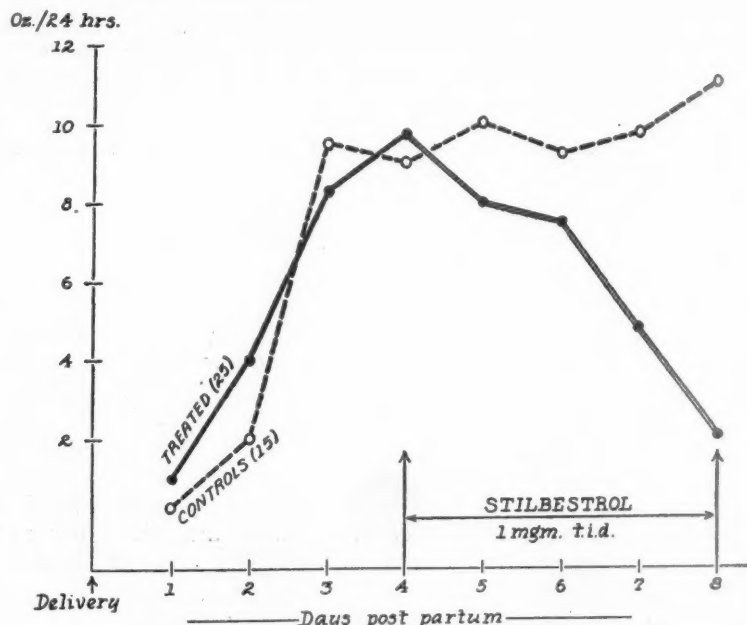


Fig. 1.—Effect of stilbestrol upon lactation. Nipples stimulated by pumping breasts during administration of drug.

*C. Treatment Following Short Period of Nursing.—*

The effect of stilbestrol upon lactation after it is well established was observed in 50 patients, who had nursed for 5 days or longer, but stopped nursing because of neonatal illness or death. As soon as the patients ceased nursing, the routine treatment for drying up breasts

was instituted. The nipples were not stimulated by pumping or suckling during the period of stilbestrol treatment. The results are shown in Table II.

TABLE II. TREATMENT FOLLOWING SHORT PERIOD OF NURSING—50 PATIENTS

	PATIENTS
1. Breast discomfort	7
2. Engorgement	7
3. Leakage during treatment	3
4. Leakage after discontinuation of treatment	4
5. No symptoms	29
Total	50

The discomfort, engorgement, and leakage during treatment lasted no longer than 36 hours in any case, and no treatment was needed because these symptoms were so mild. The cases of leakage after discontinuation of stilbestrol were relieved by additional 5-day courses of the drug. The longest interval between the 2 courses of stilbestrol was 2 weeks; this occurred in one case.

*D. Treatment During Normal Nursing.—*

This group consisted of 100 normal nursing women who previously had nursed at least one infant for three months. All of the present pregnancies and deliveries were uneventful. All infants were normal and weighed at least 3,000 grams at birth. In most instances, the mothers did not know they were under treatment.

Since we were anxious to study the effect of stilbestrol upon the amount of milk produced daily, it was measured in terms of: (1) daily infant weight, and (2) milk taken by each infant at each feeding.

(1) *Daily Infant Weight.*—Twenty patients were treated and twenty were used as controls. In the control group, the mothers nursed their infants normally.

In the treated group, as soon as the infants began to gain weight after their initial neonatal weight loss, the mothers were started on 1 mg. of stilbestrol, three times a day for 3 days.

The infants in both groups were weighed daily at the same time. They were undressed completely at the time of each weighing.

None of the infants exhibited anorexia, vomiting, vaginal bleeding or unusual breast hypertrophy.

### Results

These are shown in Fig. 2. Note that the infant weights in the treated group remained stationary during the period that the mothers were receiving stilbestrol. After the drug was discontinued, the infant weight increased, so that at the time of discharge from the hospital the average weight in the treated group was comparable to that of the control group.

(2) *Milk Taken by Each Infant at Each Feeding.*—This group included 40 treated women and 20 controls. After the infants were obtaining at least 200 grams of milk per 24 hours from the mothers, treatment was instituted. Stilbestrol was administered in doses of 1 mg., three times daily for 4 days. The infants were given no supplementary feedings during the experimental period.

The mothers were not advised of the experiment, although they received special instructions as to proper nursing—with emphasis upon the



importance of encouraging the infant to empty the breasts as completely as possible at each feeding.

*Results.* These are shown in Fig. 3. Note the drop in milk obtained by infants from treated mothers as compared to the amount of milk procured from untreated mothers.

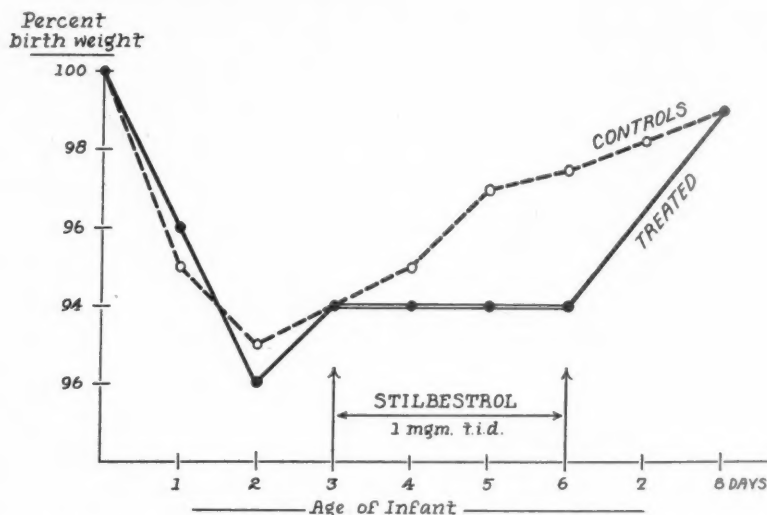


Fig. 2.—Effect of stilbestrol upon weight of infant. Drug administered to nursing mothers after onset of lactation.

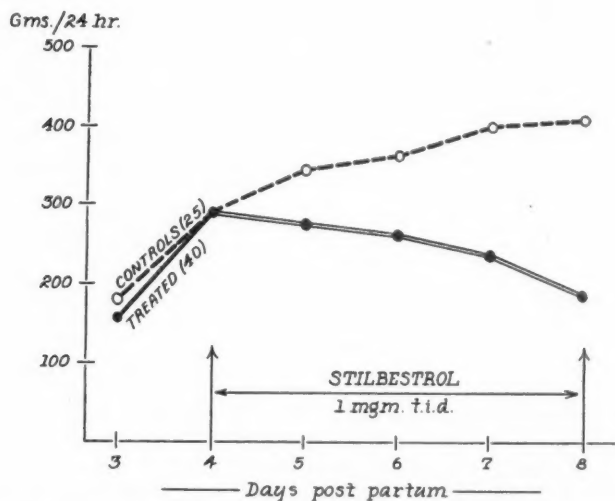


Fig. 3.—Effect of stilbestrol upon lactation. Nipples stimulated by normal suckling during administration of drug.

During the period of treatment, many mothers complained that their infants seemed hungry and would always cry. The mothers felt that they did not have enough milk for their babies.

After treatment was discontinued, most of the treated group of mothers were able to nurse their infants satisfactorily within 3 days.

### Discussion

Several interesting points arose during our experiment. First, the effect of stilbestrol upon lactation is not the same in every postpartum patient. Some were affected very slightly, while others showed a marked response to the drug in the same dosage. In fact, the usual means of mensuration, that is weighing the infant before and after each feeding, occasionally failed to demonstrate any decrease in milk secretion as illustrated in Fig. 4. From the onset of lactation, this patient was noted to have a superabundance of milk, and after the infant finished nursing, the breasts continued to leak. They were

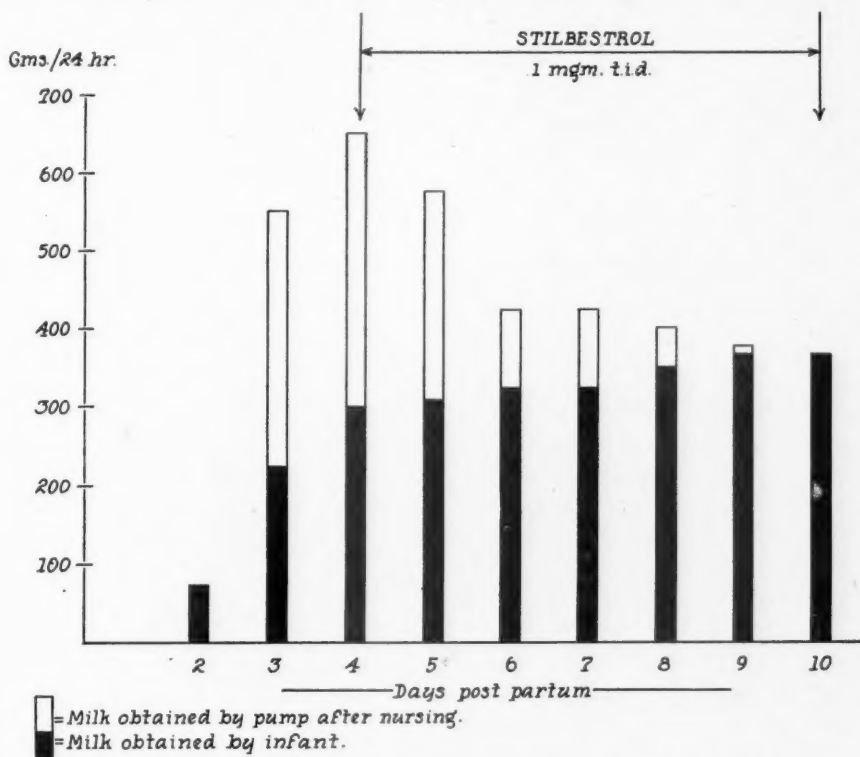


Fig. 4.—Effect of stilbestrol upon total amount of milk produced by mother.

pumped, and between 200 and 300 grams of milk were obtained in this manner after nursing. The amount of milk that was produced by this patient, as judged from the daily infant weight gain, seemed to be increasing in spite of the stilbestrol. According to routine records obtained by weighing the baby before and after nursing, this infant continued to take increasing amounts of milk in spite of the administration of stilbestrol to the mother; yet the amount of milk obtained by pumping after each nursing decreased to zero soon after stilbestrol was started. This observation may explain why some patients show no effect of stilbestrol on lactation during nursing.

In the other patients in our series, this type of observation was not possible because the breasts were readily "emptied" by the infant. In many cases we tried to pump the breasts after the infant had finished nursing, and practically no milk was obtained.

Another interesting point brought out by our study is the absence of a quantitative relationship between dose of stilbestrol and effect on lactation. We found that 1 mg. three times daily produced the same degree of depression in milk secretion as 20 mg., four times daily. Table III demonstrates this point clearly.

TABLE III. INFLUENCE OF STILBESTROL UPON LACTATION  
EFFECT OF DOSAGE

TREATED PATIENTS (40)				
NO. IN EACH GROUP	TREATMENT		MILK SECRETION (ON 8TH POSTPARTUM DAY)	
	AMOUNT TOTAL MG.	DURATION DAYS	GM. (AVERAGE)	% DEPRESSION
15	36	4	186	54
10	56	5	160	60
6	203	6	160	60
9	426	5.5	170	58
CONTROLS (25 NORMAL POSTPARTUM WOMEN) 408				

Showing the relative amount of milk secretion on the last day of postpartum treatment by patients receiving stilbestrol, compared with the average amount secreted on the eighth postpartum day by the control group.

NOTE: (a) Depression of milk secretion following treatment. (b) That there is no direct relationship between amount of drug given and degree of depression of milk secretion.

The other point of interest is the ability of postpartum women to take varying doses of stilbestrol by mouth with no demonstrable untoward effects. None of the mothers or infants in our series showed any unusual signs or symptoms that could be attributed to the stilbestrol.

### Summary and Conclusions

The effect of stilbestrol upon lactation was studied in 250 normal postpartum women under 4 types of circumstances, with the following conclusions:

1. Stilbestrol is effective in aiding cessation of lactation.
2. Stilbestrol given to normally nursing postpartum women will depress milk secretion in spite of normal suckling.
3. In rare cases, stilbestrol may have no obvious effect upon lactation.
4. The dose of stilbestrol bears no quantitative relation to its effectiveness in depressing milk secretion.

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## THE CATHETER METHOD FOR CONTINUOUS CAUDAL ANESTHESIA

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THE introduction of continuous caudal anesthesia in obstetrics by Edwards and Hingson has elicited widespread interest, and as a result, a number of modifications of their original technique have been reported. One of these is the employment of a ureteral catheter instead of an inlying steel needle for the administration of the anesthetic substance.

In 1942, Manalan<sup>1</sup> described his method for single injections, and in 1943, Adams, Lundy and Seldon<sup>2,3</sup> reported their observations on the use of an inlying ureteral catheter for continuous caudal anesthesia. Siever and Mousel,<sup>4</sup> who used a 13 gauge needle and a No. 5 ureteral catheter, reported satisfactory results in 96 per cent of their series of 300 obstetric patients. Irving,<sup>5,6</sup> employed a 15 gauge needle and a No. 4 catheter, and for difficult insertions used an 18 gauge needle as a guide with a 15 gauge needle slipped over it.

This report describes our procedure, which differs from other methods previously reported in that a wire guide is used to facilitate the introduction of the catheter.

### Method

*Indications.*—Caudal anesthesia for obstetric patients is instituted only when labor has made definite progress. The primiparous cervix should be dilated at least 4 cm., while 2 to 3 cm. is sufficient in the multiparous patient. Uterine contractions in *all* instances should be at intervals of 3 minutes or less.

*Preliminary Preparation.*—Premedication with a barbiturate—usually 3 grains of nembutal or seconal are given 15 minutes beforehand. The bladder is emptied, and the large bowel cleansed with a low enema.

*Technique.*—The patient is placed face down with the hips elevated by a large pillow. The sacral region is painted with tincture of phenol or merthiolate and draped with sterile towels. The sacral hiatus is identified and a wheal is raised in the overlying skin with local anesthetic solution. Metycaine, 1.5 per cent, has proved satisfactory. A 22 gauge 2-inch needle is connected to the syringe and passed through the skin wheal and the sacrococcygeal ligament into the caudal canal. When the caudal space is entered, a characteristic "jump" is felt as the needle point traverses the depth of the caudal canal and strikes the anterior wall.

Five c.c. of 1.5 per cent metycaine solution are injected to serve as a test for undue reaction, and to render the remaining portion of the procedure painless. The needle is removed and a 15 gauge 3-inch needle



is introduced, bevel-up, into the canal. As soon as the sacrococcygeal ligament is penetrated (this is readily discerned with the rigid needle), the hub is depressed and the needle advanced for a distance of 5 to 6 centimeters. It is important to avoid scraping the anterior wall of the canal, where many blood vessels may be encountered.

The bevel of the needle is now directed downward and the stilet removed. If neither blood nor spinal fluid can be aspirated, an additional 5 c.c. of metycaine is injected, and if the 15 gauge needle is in proper position, it will flow in easily.

An autoclaved No. 4 ureteral catheter with wire guide is now made ready for insertion. The wire guide remains in the catheter, but *before insertion* it is withdrawn for a distance of 2 cm. from the catheter tip. This retains the advantage of the guide, while providing a soft, flexible tip which is not likely to penetrate the dura or blood vessels.

The catheter is passed through the needle until its tip is 3 to 4 cm. beyond the needle point. The needle is withdrawn over the catheter and the depth of insertion adjusted. The catheter may be advanced or withdrawn at this juncture as long as the guide has not been removed. The average patient requires a depth of 12 cm., while 10 cm. will suffice for a thin person. Obese patients must have the catheter inserted 15 cm. to insure its remaining in the canal. Distances are from the catheter's exit at the skin and are easily determined with a calibrated catheter.

The wire guide is now withdrawn and the catheter strapped firmly in place with adhesive tape. A 22 gauge  $\frac{3}{4}$ -inch short-bevel needle is inserted into the distal tip of the catheter and aspiration attempted with a syringe. If neither blood nor spinal fluid appears the needle is connected by means of a Luer-Lok fitting to a rubber tube leading to the metycaine bottle. A two-way automatic valve and a 10 c.c. syringe complete the closed system.

Fifteen c.c. of metycaine are injected through the catheter, making a total initial dosage of 25 cubic centimeters. This often suffices to relieve all uterine pain and produce skin anesthesia up to the umbilicus. If not, 10 to 15 c.c. more may be injected. Subsequent injections of 20 c.c. are given, whenever the patient feels her pain returning. The skin level of anesthesia is best maintained at, or slightly below, the umbilicus.

#### Observations and Precautions

1. *Stage at Which Caudal Anesthesia Is Instituted.*—As emphasized by McCormick,<sup>7</sup> it is most practicable to delay institution of caudal anesthesia until labor is well advanced and the pains are at 2- to 3-minute intervals. This is advantageous because it forestalls the necessity of discontinuing the procedure because contractions have stopped. It also shortens the duration of anesthesia, thus diminishing the total dosage and reducing the possibility of a toxic effect on mother or baby.

2. *Use of the 15 Gauge Needle.*—The needle point must avoid the anterior wall of the caudal canal or troublesome bleeding will ensue. The rigid needle is more readily controlled than one of malleable construction.

Test aspirations for blood or spinal fluid should be made with the needle in both bevel-up and bevel-down positions. The needle should be rotated to the bevel-down position *before* introducing the catheter as a precaution against shearing the catheter tip. This occurred once

in our series. The needle was bevel-up and a 1 cm. piece was cut off by the sharp, up-turned bevel. At the patient's request, no attempt was made to recover the tip, and she has experienced no ill effect. We believe such an accident is less likely to occur if the needle is bevel-down when the catheter is inserted.

When the 15 gauge needle and the catheter are *both* in the caudal canal, there are two things to avoid: (1) the needle *must not* be inserted farther, and (2) the catheter *must not* be withdrawn until the needle has first been removed. Either of these tends to shear the catheter.

3. *Use of the Ureteral Catheter.*—It is unsafe to insert the catheter with the wire guide *without first withdrawing the guide* 2 cm. from the catheter tip. If this precaution is not observed the subarachnoid space will surely be entered.

Test aspirations for blood or spinal fluid *must* be made through the catheter after it has been placed. In spite of all precautions, we have aspirated blood a number of times and spinal fluid once.

4. *Asepsis.*—Scrupulous care must be taken in the sterile preparation and draping of the sacral area. Sterile gloves should be worn by the operator, and subsequent injections must not contaminate the syringe piston.

5. *Level of Skin Anesthesia.*—The catheter method produces higher levels of skin anesthesia than are obtained with the needle. For this reason, the initial injection should not exceed 25 cubic centimeters. If necessary, this may be increased until the skin level is at the umbilicus. Several of our earlier catheter caudal blocks produced skin anesthesia to the clavicles. One patient experienced numbness of the arm and hand, but there appeared to be only slight paralysis of the intercostal muscles. This has not occurred since limiting our initial dosage to 25 cubic centimeters.

6. *Prevention of Urinary Distention.*—If the anesthetic is continued for longer than 6 to 8 hours, the bladder must be catheterized. Frequently, it may be emptied by gentle suprapubic pressure with the patient on a bedpan. This precaution is especially important in preventing postpartum cystitis and urinary retention.

7. *Barbiturate Administration.*—It is generally accepted that barbiturates lessen the toxicity of the local anesthetic agents. It is probably well to repeat the nembutal or seconal at intervals of 6 to 8 hours, to offset loss of the drug's effect by metabolism.

8. *Excessive Drop in Blood Pressure.*—Although this occurred in not more than 2 per cent of our patients, measures for control are kept at hand. Administration of oxygen is of most benefit, but neosynephrine and ephedrine are good.

### Results

Satisfactory anesthesia was obtained in 277 of our first 300 unselected cases, and there were only 6 (2 per cent) complete failures. Twenty-three (8 per cent) required supplemental anesthesia. Light supplemental anesthesia was administered to an additional 26 patients, because they wished to be asleep in the delivery room. With 2 exceptions, the caudal blocks were administered by 7 different members of our resident staff.

Nine cesarean sections and 5 gynecologic operations are included in our series. The remaining 286 are vaginal deliveries consisting of 10

spontaneous, 251 low forceps, 7 midforceps, 2 high forceps, 12 breech, and 4 version and extraction cases. Each of the last 4 necessitated deep inhalation anesthesia to provide sufficient relaxation of the uterus.

There were no maternal deaths. Seven babies were lost, a fetal mortality of 2.4 per cent, but none of these was attributable to the caudal block.

Complications resulting from the caudal anesthesia occurred in 2 patients. A superficial skin infection developed at the site of the catheter's exit in one, and in another paralysis of the anal sphincter persisted for 10 days. Sixteen patients had urinary retention for more than 24 hours.

### Comments

A number of advantages may be ascribed to the catheter method of continuous caudal anesthesia.

1. *Safety*.—A soft, flexible catheter is undeniably safer than a steel needle. Needle breakage is now rare, but there is always the possibility of a shift in position of the patient. Any such movement often dislodges an inlying needle, with the result that subsequent injections no longer reach the caudal canal. More dangerous, however, is the risk of piercing the dura or blood vessels. Once the catheter has been properly placed, it cannot be dislodged and subsequent injections can be made safely and effectively.

2. *Position of the Patient*.—Complete freedom of movement is permitted the patient. Descent of the fetal head often has been impeded by the lateral position necessitated by the needle method. The catheter allows the patient to remain on her back with safety. She may be transported to and from the delivery room without interrupting the anesthetic.

3. *Facility of Insertion*.—We have found that it actually is easier to manage the rigid 15 gauge needle than the malleable type. This is particularly true within the caudal canal, where the operator must be able to control the needle point.

4. *Obesity*.—Caudal anesthesia with the inlying needle method is often impossible in the obese patient. This is because the usual malleable needle is not long enough to penetrate the pad of fat over the sacrum and remain in the caudal canal. Moreover, the needle is readily dislodged by the motion of the fat itself. If the obesity does not prohibit locating the canal, a catheter may be inserted to the proper level and anchored securely in position.

### Summary

1. A technique for the catheter method of continuous caudal anesthesia is described.

2. A series of 300 unselected cases is reported. There were 6, or 2 per cent, complete failures, and 23 patients (8 per cent), who required supplemental anesthesia.

3. There were no maternal deaths. Seven babies were lost, the deaths of none of these could be attributed to caudal anesthesia.

4. The catheter method possesses the advantages of increased safety, freedom of movement by the patient, and facility of insertion.

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2398 SACRAMENTO STREET



## SIMILARITY OF MOUTH AND VULVAR LESIONS

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THE purpose of this presentation is to point out a clinical correlation of lesions common to the mucosa of the mouth and to the mucosa of the vulva. A brief review of embryology will illustrate that there are structural anatomical similarities between the mouth and the vulva.

In the early embryo, the foregut and the hindgut end blindly. The pharyngeal membrane separates the stomodeum from the anterior end of the foregut; in the breech, the intestinal, urinary, and genital tracts open into a common space, the cloaca, which is separated from the outside by the cloacal membrane. The pharyngeal membrane is formed by fusion of the stomodeal ectoderm and foregut entoderm; the cloacal membrane consists of ectodermal cells and entoderm of the hindgut. Both of these membranes disappear in the early weeks of embryonic development.<sup>1</sup> The mouth is developed from the stomodeum and partly from the floor of the foregut. The vulva is of ectodermal origin and surrounds the exits of the urinary, vaginal, and rectal orifices. The salivary glands develop as buds from the epithelium of the mouth of the embryo between the fourth and ninth weeks. Salivary secretions are not fully established until the fourth month of infancy.<sup>2</sup> Bartholin's glands are developed by the third month and contain mucus by the fifth month of fetal life.<sup>3</sup> Secretions from the parotid, submaxillary, sublingual, and labial glands of the mouth are alkaline. The mucoserous discharge from Bartholin's glands is also alkaline. Secretions from both the oral and vulvar glands are subject to control of the autonomic nervous system.

Sweat glands are of interest in that the vermilion borders of the lips and the labia minora are the only surface areas of the female body completely devoid of the small eccrine sweat glands.<sup>4</sup> The large apocrine sweat glands, associated with hair follicles, are in abundance on the mons veneris, the labia majora, the perineum, and to a much lesser degree in the skin about the lips. Sebaceous glands normally open into hair follicles, but on the vermilion borders of the lips and on the hairless labia minora they open directly on the surface.

The vestibule of the mouth, that area between the teeth and gums and the lips and cheeks, and the vestibule of the vulva, the space between the labia minora, are quite similar with regard to temperature, degree of anoxia, and texture of the surrounding tissues. With nasal breathing, there is very little more oxygen in the mouth than is ordinarily present in the vulvovaginal area. The lips and the labia minora are particularly well supplied with nerves, blood, and lymph vessels.

Congenital abnormalities in the mouth are usually cleft or fusion defects while the most common anomalies of the female genitalia are hymenal or Müllerian duct deformities.

For satisfactory examination of either the vulva or mouth, it is important to have the patient in a proper position with adequate illumination and satisfactory instruments for visualization. For protection to himself and to his patient, the physician should wear rubber gloves for palpating lesions in the mouth or on the vulva. Regional lymph gland palpation is of distinct value in both areas.

### Color of the Mucosa

With few exceptions, systemic factors influencing circulation to the mucosa of the mouth and vulvovaginal area cause similar color changes. Anoxia due to anesthesia, pulmonary or cardiac disease results in cyanosis of the vulvar and oral mucosa. Anemia causes pallor in both areas. Jaundice gives a yellowish color to the mucosa. Certain poisons such as carbon monoxide, sulfanilamide, and the aniline dyes change the color of the circulating blood by reducing oxyhemoglobin. Polycythemia results in a rich red discoloration of both the oral and vulvovaginal mucosa.

### Changes in Menstruation, Pregnancy, and the Menopause

Of particular interest to the obstetrician and gynecologist are the mucosal changes found in the menstrual cycles, in pregnancy, and in the menopause. Systemic premenstrual vascular changes bring about submucosal engorgement and redness in the mouth. Premenstrual engorgement of the vulvar mucosa is usually a deeper, reddish blue. Premenstrual edema of the lips, face, and vulva occasionally occur. Cyclic endocrine changes influencing the oral mucosa may give rise to hyperemia and bleeding of the gingivae in association with menstruation. This condition is known as stomatitis dysmenorrheica.<sup>5</sup>

Oral changes associated with pregnancy are those of hypersecretion and tissue proliferation. Early in pregnancy salivary secretions are increased. Ptyalism is an annoying, contributory factor in the early vomiting of pregnancy. The gravid patient often experiences changes in taste perception and appreciation. A proliferative marginal gingivitis occasionally occurs in pregnancy. The overgrowth of the gum margins in stomatitis gravidarum may be extensive enough to cover the teeth. The micropathology of this pregnancy tumor is that of an angiomatous proliferation in fibrous tissue. The gingivae generally return to normal after delivery.<sup>6</sup> Other benign tumors of the gums frequently enlarge during pregnancy. If these tumors are removed during gestation, the recurrence incidence is greater.<sup>7</sup> Secretions from the genital glands are more profuse during pregnancy. Papillomas and condylomas recur more frequently when they are removed from the pregnant patient. The smooth tongue and the pale buccal mucosa of the last trimester of pregnancy are usually associated with hypochromic anemia. The vulvar mucosa of the gravid patient may be pale, but venous congestion of the vagina and cervix gives rise to blueness of that mucosa.

The atrophic menopausal changes in the mucosa of the mouth and vulva are quite similar. The menopause is accompanied by a decrease in salivation and in vaginal secretions. The mucosa becomes dry, glazed, and much less resistant to infection. Older women frequently complain of dryness and burning of the mouth and of irritation and itching of the vulva. Estrogenic therapy will give relief of symptoms from both areas. The estrogenic hormone increases cell activity and specialization. Resistance to mouth and vulvar infections is heightened by activation of the mucosa with estrogens.<sup>8,9</sup> However, neither estrogenic nor vitamin therapy is indicated in the patient with definite kraurosis or leucoplakia of the vulva. These advanced premalignant skin changes require vulvectomy as the safest method of management.

### Blood Dyscrasias

In severe relapses of pernicious anemia, bald atrophic tongue, ulceration of the lips and buccal mucosa, and superficial ulceration of the vulva occur along with hyperpigmentation of the surrounding skin. There is evidence to indicate that these mucosal changes are due to a combination of achlorhydria and vitamin B deficiency.<sup>10, 11</sup> In aplastic anemia and in leucemia, stomatitis and vulvitis are manifested by bleeding gum margins, ulceration of the oral and vulvar mucosa. Ulcerations in both areas are frequently infected with fusospirochetal organisms.

### Local Infections

One of the most common surface infections of the oral and vulvovaginal mucosa is thrush, or moniliasis, due to the *Monilia albicans*. *Monilia* will not grow on healthy mucous membrane, but thrive on mucosa which is subjected to trauma or lowered resistance. Poorly nourished infants, diabetic women, and anemic pregnant patients are good candidates for moniliasis. In methods of resuscitation, it is well for the obstetrician not to traumatize the mouth of the infant with his gloved hand which has been contaminated by the vaginal discharges of the mother.

Diphtheria develops in an alkaline medium and in an abundance of air. The disease is characteristically one of the pharynx. However, oral and vulvovaginal diphtheria occasionally occur.

Tuberculous ulceration, present on the vulva or in the mouth, is usually found in the patient with far-advanced pulmonary or enteric tuberculosis.

Chancroid is a disease of the vulva which can be transplanted to the oral mucosa.

Gonorrheal stomatitis is rare; gonorrheal vulvovaginitis is the most common of venereal diseases.

Psoriasis, herpes simplex, lichen planus, and impetigo are local diseases, which may affect either the mouth or the vulva.

Skin irritation of the vulva and perineum secondary to a chronic, profuse alkaline cervical discharge compares with changes seen in lips

and chins which have been subjected to constant dribbling from the mouth.<sup>12</sup>

Vincent's fusospirillae are common secondary invaders of vulvar ulceration just as they are of lesions in the mouth.

### Tumors

Benign and malignant tumors of connective tissue, blood and lymph vessels, and epidermis occur in the mouth and on the vulva. There is no definite relationship between the two except that syphilitic leucoplakia is quite common to both areas. Stokes' statement, "on finding leucoplakia, look backward toward syphilis and forward to cancer"<sup>13</sup> can apply to both areas. Diffuse fibromatosis of the gingivae has the gross and microscopic characteristics of venereal condylomas.

### Systemic Diseases

The most serious systemic disease common to the vulvar and oral mucosa is syphilis. Breaks in the mucosa are not necessary for inoculation with *Treponema pallidum*. The labia majora are second only to the cervix as the initial site of syphilis in the female.<sup>14</sup> The lip is the most frequent extragenital area for chancre. The most open and infectious lesions of secondary syphilis, i.e., condylomata lata and mucous ulcers, are found on the vulva and in the mouth. Until secondarily infected, syphilis of the mucous membrane is fairly typical and usually painless. Macular and erosive syphilides are found on the mouth or labia minora; papular syphilis is common on the vulva, but rare in the mouth; ulcerative and sclerous syphilides occur in both areas. Hutchinsonian teeth and rhagades are evidence of congenital syphilis.

Diabetic stomatitis and vulvitis are quite similar. The mucosa membrane in both areas is dry, parched, and deep red in color. The patient complains of a burning sensation in the mouth and on the vulva.

In uremic stomatitis, the mouth changes are more profound than in the vulva. The tongue becomes dry, thick, and brown coated. The oral mucosa is inflamed and ulcerated. The gingivae bleed easily, and the uvula becomes swollen. The vulva frequently becomes edematous, reddened, and ulcerated. The discharges from the mouth and from the vagina have a uriferous odor.

In recent years, physicians and nutritionists have made extensive studies in vitamin deficiency diseases. A scientific basis has been established for the reliance the old family physician placed on the tongue as an indicator of dehydration and malnutrition. Changes in the dorsum of the tongue, the buccal mucosa, and lips often reflect vitamin deficiencies secondary to gastroenteric and febrile diseases. Gynecologists have noted the effects of vitamin deficiencies on the mucocutaneous surfaces of the vulva.<sup>15, 16</sup> B<sub>2</sub>, or riboflavin, deficiency is manifested by a red, raw tongue, shiny, red mucosa of the lips and buccal surfaces, and an angular cheilitis.<sup>17</sup> A similar shiny redness and rawness of the vulva occurs. Ariboflavinosis favors the development of monilial infection.



Vitamin B<sub>2</sub> is specific therapy. The lesions will not respond to nicotinic acid alone. Pellagra, due to a deficiency in nicotinic acid and other factors of the B complex, produces soreness, redness, and ulceration of the tongue, gums, oral mucosa, and lips, vulvovaginitis, thickening and pigmentation of the skin. Pellagra favors secondary infection with Vincent's organisms.<sup>18</sup> An adequate diet supplemented with nicotinic acid and brewers' yeast will initiate tissue repair of both the oral and vulvar lesions. With the widespread use of estrogens and with evidence that they stimulate tissue regeneration, it is of interest to note that Ashworth and Sutton found that "estrogens do not aid in the utilization of the vitamin B Complex."<sup>19</sup> According to their evidence, estrogens given to individuals with subclinical vitamin B complex deficiencies caused the appearance of characteristic polyneuritis, pellagra, and cheilitis.

### Conclusions

There is a structural embryologic, anatomic, and physiologic similarity between the mucosa of the mouth and vulva. Certain local and systemic infections influence both areas. The patient may complain of symptoms from only one area, when similar lesions can be found both on the vulva and in the mouth. The importance of a thorough examination of both areas is stressed. Women frequently consult the doctor early about mouth lesions, but they are somewhat reluctant to seek advice at the onset of genital symptoms.

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## FIVE HUNDRED CONSECUTIVE CESAREAN SECTION OPERATIONS\*

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**I**N this report and analysis we have studied a group of 500 consecutive cesarean sections performed at Chicago Lying-in Hospital from March 1, 1938, to March 6, 1942. This series of cesarean sections constitutes a complementary third group of 500 cases operated upon consecutively in this institution from May, 1931, to March, 1942. The prior two groups totaling 1,000 cases were analyzed by Daily in 1939. Interest lies in comparison of results; hence, in summary, certain factors in statistical change will be noted.

From March 1, 1938, to March 6, 1942, there was a total of 11,281 deliveries at Lying-in Hospital, giving a section incidence of 4.43 per cent for this particular group and period.

Thirty-three operators were responsible for the surgery in the series. The departmental staff of Lying-in Hospital consisting of full-time members and residents handled 398 of the cases. The remaining 102 cases (20.4 per cent) were operated upon by members of the practicing courtesy staff. No one individual operated upon more than 13.8 per cent of the cases (69).

### Types of Operative Procedure

455 Laparotrachelotomies	91.0%
205 Laparotrachelotomies with tubal ligation	41.0%
2 Classics with tubal ligation	
1 Laparotrachelotomy with cornual resection	
37 Cesarean hysterectomies	7.4%
4 Classical cesarean sections	0.8%
4 Vaginal cesarean sections	0.8%
<i>First Section</i>	
306 Cesareans	61.2%
271 Laparotrachelotomies	
28 Cesarean hysterectomies	
3 Classics	
4 Vaginal	
<i>Second Section</i>	
167 Cesareans	33.4%
159 Laparotrachelotomies	
7 Cesarean hysterectomies	
1 Classical	
<i>Third Section</i>	
26 Cesareans	5.2%
24 Laparotrachelotomies	
2 Cesarean hysterectomies	
<i>Fourth Section</i>	
1 Laparotrachelotomy	0.2%

### Maternal Mortality

There were two deaths in the series for a percentage of 0.4. One of these patients died of cerebral hemorrhage and/or eclampsia. The patient was considered a poor risk at the time of operation. No anesthetic was required. The other death resulted from hemorrhage and shock following cesarean section in a case of total placenta previa.

\*Presented at a meeting of the Chicago Gynecological Society, April 21, 1944.

### Fetal Mortality

There were 35 neonatal and 11 intrapartum deaths; giving a fetal mortality of 9.2 per cent for the 500 sections. In the neonatal group 22 of the cases were premature, 10 were previable (91.5 per cent). In the stillborn group, 4 cases were premature and 4 previable (72.7 per cent). In both the neonatal and intrapartum series, the antecedent maternal pathology was largely toxemia, abruptio placenta and placenta previa. It was noted as 10 cases of toxemia, 5 cases of abruptio placenta, and 9 cases of placenta previa in the neonatal deaths; and 2 cases of toxemia, 4 cases of abruptio placentae, and one of placenta previa in the intrapartum deaths.

### Maternal Morbidity

The morbidity standard used has been that of the American Committee on Maternal Welfare. The mortality figure in the series was included in the morbidity evaluation. There were 155 febrile cases using this index (31 per cent): 70.9 per cent of the morbidity (110 cases) was genital in origin; 12.9 per cent (20 cases) resulted from urinary tract infections; and 3.8 per cent of the morbidity (6 cases) was attributed to respiratory tract infections. Transfusion reactions, thrombophlebitis and wound infections about equally accounted for 7.1 per cent of the morbidity (10 cases), and 9 other cases were, in total, responsible for the remaining 5.8 per cent of the morbidity with various diagnoses other than these listed.

### Effect of Labor and Ruptured Membranes on Morbidity

We have been interested in this particular feature of this study not only because of its primary importance but, also, because of the stress laid on such morbidity findings in some of the contributory literature and in clinical consideration. For these reasons, we have analyzed the group in somewhat more detail than is usual.

In the 500 sections, 300 cases were neither in labor, nor had ruptured membranes (60.0 per cent). Eighty-six of these sections became febrile (28.6 per cent). Of the total number of sections, 164 (32.8 per cent) were in labor; 59 (35.9 per cent) of these were febrile. A total of 119 cases (23.8 per cent) had ruptured membranes and 42 of these were febrile (35.3 per cent). Thirty-six cases were not in labor and had ruptured membranes; 11 of these became febrile for a percentage of 30.5. Eighty-three cases both were in labor and had ruptured membranes (16.4 per cent); of this group 31 were febrile (37.3 per cent). With membranes unconsidered, 56 cases were in labor less than 12 hours, and 49 cases were in labor more than 12 hours and were afebrile. The morbid cases under the same conditions about balanced—31 and 28. In the instance of ruptured membranes for less and more than 12 hours, disregarding labor, the afebrile cases were noted as 45 and 32; the febrile cases 21 and 21. In the cases both in labor and with ruptured membranes for less and more than 12 hours, the febrile per-

centages of 32.2 and 46.1, respectively, gave an indication of the higher morbidity in such cases. Further, with only one exception, the morbid percentages throughout the group were noted to be higher where the element of time increased in relation to labor. Though the number of cases for comparison was small, it was likewise noted that morbidity increased by an approximate one-fourth when labor accompanied ruptured membranes, 37.3 per cent and 30.5 per cent, respectively. Moreover, it is significant that the febrile percentage of 28.6 noted in those cases operated upon under the conditions of intact membranes and no labor was within 1 per cent of the lowest morbidity evaluation found under any conditions.

#### Effect of Toxemia on Morbidity

Out of a total of 92 cases of toxemia, 46 cases were febrile (50 per cent). In the sections for abruptio placenta, toxemia being frequently a common factor, 5 cases out of 13 were morbid (38.5 per cent).

#### Effect of Secondary Section on Morbidity

Of the 271 laparotrachelotomy first section cases, 95 were morbid (35.1 per cent). Of the 159 second section cases, 40 were febrile (25.1 per cent). Out of the 24 cases of third section, 3 (12.6 per cent) were febrile. Thirteen of the 37 cesarean hysterectomies were morbid (35.1 per cent); 3 of the 4 vaginal sections were morbid (75 per cent); and one of the 4 classical sections was morbid (25 per cent). The decreasing morbidity noted in the second and third multiple section cases was due to the fact that they were usually elective; the conditions which contributed to morbidity at first section not being present on secondary section.

#### Indications for Cesarean

There was a total of 306 primary sections in the series (61.2 per cent). This is an inclusive figure comprising the total of laparotrachelotomies, cesarean hysterectomies, classical and vaginal sections.

*Dystocia and Disproportion.*—Cephalopelvic disproportion, 75; Contracted pelvis, 30; Fibroid uterus, 16; Prolonged labor with inertia, 9; Vaginal plastics, 9; Elderly primipara, 4; Stillbirth history, 4; Cervical dystocia, 3; Contraction ring, 2; Transverse, 2; Uterine anomalies, 2; Dystrophy-Dystocia Syndrome, 1; Brow, 1; Face, 1; Ovarian cyst blocking pelvis, 1.—160 cases (32.0 per cent).

*Toxemias.*—Pre-eclampsia, 37; Eclampsia, 8 (8.0 per cent); Hypertension, 22; Nephritis and Pyelitis, 13 (7.0 per cent). Total 75 cases (15.0 per cent).

*Hemorrhage.*—Placenta previa, 39; Abruptio placenta, 13; Ruptured uterus, 2.—54 cases (10.8 per cent).

*Cardiac.*—12 cases (2.4 per cent).

*Other Indications for Primary Section.*—Diabetes, 2; Pulmonary tuberculosis, 1; Premature rupture of membranes with intrauterine death of fetus, 1; Spastic paralysis, 1.—5 cases (1.0 per cent).

The predominating indication for operating the remaining 194 (38.8 per cent) cases was previous section. This was combined with a desire to sterilize in many instances; in others, the primary indication carried



over and enhanced the indication for secondary section. Cases of contracted pelvis, hypertensive vascular disease, nephritis, and certain chronic diseases are illustrative of continuing concomitant indications which reinforced the indication for secondary section. However, for the purpose of later comparison, when continuing, recurrent or variant pathology was noted as a distinct factor in the indication for secondary section, this indication was then considered as primary in analysis. Thus, in this group there were 113 cases (22.6 per cent) having disproportion and dystocia as an indication for repeat section, 17 cases of toxemia (3.4 per cent), five cases with vaginal hemorrhage (1 per cent), three cardias (0.6 per cent), and four cases of miscellaneous pathology (0.8 per cent). The remaining 52 cases (10.4 per cent) had no other significant noted indication for section save previous cesarean.

#### Previous Section and Sterilization

Of 167 cases having had 1 previous section, 113 were sterilized (67.7 per cent). Twenty-six cases had had two previous sections; all of these were sterilized (100 per cent). One case had a fourth section; this case was sterilized (100 per cent). Of the 271 primary laparotomies, 77 (28.4 per cent) were sterilized by tubal ligation (Madlener).

#### Stillbirths

There were 310 multiparas in the series (62 per cent). In 38 of these, there was a history of one or more stillbirths (12.2 per cent). The obstetric history in the majority of these cases rather closely followed the expected pattern, i.e., contracted pelvis, prolonged labor, toxemia, or one of the hemorrhagic accidents. This type of history frequently constituted an influencing factor in the indication for operation.

#### Period of Gestation

Two hundred and forty-eight cases (49.6 per cent) were 36 to 40 weeks; 103 cases (20.6 per cent) were 40 weeks; 79 cases (15.8 per cent) were 41 to 44 weeks; 69 cases (13.8 per cent) were less than 36 weeks; 1 case (0.2 per cent) was over 44 weeks.

The indications for interference in the 69 cases under 36 weeks were almost entirely abruptio placenta, placenta previa, or toxemia.

#### Anesthesia

Local alone—280 cases (58 per cent); local and cyclopropane—62 cases (12.4 per cent); local and ethylene—12 cases (2.4 per cent); local and ethylene and ether—3 cases (0.6 per cent); cyclopropane—110 cases (22 per cent); ethylene—8 cases (1.6 per cent); ethylene and ether—19 cases (3.8 per cent); ethylene and ether and cyclopropane—2 cases (0.4 per cent); cyclopropane and ether—2 cases (0.4 per cent); cyclopropane and ethylene—1 case (0.2 per cent); none—1 case (0.2 per cent).

A solution of one-half per cent novocain in local infiltration held predominant position as an anesthetic agent. As complementary anesthesia, cyclopropane was favored over ethylene or ether. Cyclopropane alone was used in over one-fifth of the cases, the indications usually being an uncontrollable or nervous patient, or necessity for rapid operation.

### Summary

The maternal mortality in the first two series comprising 1,000 cases of cesarean section was 0.8 per cent. In the last 500 cases, it was 0.4 per cent, demonstrating a 50 per cent decrease. Maternal mortality for the 1,500 cases was 0.66 per cent. Four of the deaths in the first 1,000 cases resulted from infection of genital origin. No deaths in the last group were attributed to puerperal sepsis, as attested by autopsy.

The morbidity in the earlier series was 43.8 per cent. The morbidity in this latter group was 31 per cent. This was a decrease of 29 per cent in total morbidity in the last four years. The combined morbidity for the entire 1,500 cases was 39.5 per cent.

Fetal mortality was noted to be 6.7 per cent in the first 1,000 cases. In this latter series, it had risen to 9.2 per cent. Part of this rise in fetal mortality was due to a rise in the incidence of section in toxemias. In the first 1,000 cases, 12.3 per cent of the sections were performed with the indication toxemia and related conditions. In this latter group 18.4 per cent of section incidence was attributed to toxemia. The necessity for early interference in the fulminating toxemias increased fetal mortality.

The incidence of section in the earlier group was 5.5 per cent. The recent series showed a section incidence of 4.43 per cent; the incidence decreased approximately 20 per cent in comparison.

There was a variance in the relationship of indications for section between the first series and this latter. The greatest disparity was noted in three groups. Multiple sections increased from 27.9 per cent in the first series to 38.8 per cent in the latter. More section cases are returning for reoperation. Cardiac pathology as an indication for section was noted as 10.4 per cent in the first 1,000 sections. It was down to 3 per cent in this last study. Cesarean section incidence in heart disease is on the decrease for two reasons. Many of these cases where pregnancy is a distinct hazard are being interrupted early with sterilization, or with helpful contraceptive advice; and many others under careful medical observation and control are being carried to late viability or term with subsequent safe vaginal delivery.

Toxemia, as an indication for interference, accounted for 12.3 per cent of the sections in the earlier series; in the last 500 cases, this indication had risen to 18.4 per cent. This reflects the tendency to adopt an active obstetric attitude toward the problem of severe and unresponsive toxemia.

### Conclusions

The maternal mortality and morbidity of cesarean section in Chicago Lying-in Hospital have shown a continuous decrease from 1931 to 1942. It is probably not yet irreducible.

Though the indications for cesarean section have become in the past decade probably somewhat more comprehensive, the incidence of cesarean section has decreased. Careful selection of cases has operated in favor of vaginal delivery, and primary elective section for the purpose of sterilization has, in the main, been supplanted by postpartum tubal ligation.

The low flap transperitoneal section is the operation of choice in this institution. General procedure and technique have not changed, but critical attention as to indication and time for interference has contributed to improve statistics.

I wish to express my appreciation to Dr. W. J. Dieckmann for his helpful criticism in the preparation of the manuscript.

### Discussion

DR. PHILIP H. SMITH.—The members of our department at the Evanston Hospital have been pleased with our results in cesarean section. It is, therefore, satisfying when I note the close similarity between several of the important figures and percentages in Dr. Free's report and our own statistics.

In a fifteen-year period—1929 through 1943, we have delivered 13,575 women. The incidence of cesarean section in this group was 3.88 per cent, while Dr. Free reports 4.43 per cent incidence. We regularly do the low cervical operation, and during this period less than a dozen classical operations were done.

Our maternal mortality is 0.9 per cent as against 0.4 per cent for the recent Lying-in series. The deaths in our group have been due to pulmonary embolism, postoperative hemorrhage, peritonitis and toxemia with pneumonia.

Our fetal mortality of 9.3 per cent compares with Dr. Free's figure of 9.2 per cent. These percentages are almost three times that for the fetal mortality when patients are delivered otherwise. Dr. Free has made it clear, however, that toxemia and nonviable states in bleeding cases, largely account for this.

Our morbidity is 33 per cent, while in the report it was reported at 31 per cent. I believe this figure to be largely dependent upon the length of labor and whether or not the membranes are ruptured.

While recognizing the important place abdominal delivery holds, there can be no doubt it is often done too frequently, and when the proper conditions cannot be met. While it may often be the easiest way out of a difficulty, it is not necessarily the safest and best. A figure in the vicinity of four per cent seems to be a fair one. The men at the Lying-in have only slightly exceeded 4 per cent, which is a reduction from their earlier group in which the incidence was 5.5 per cent. Our incidence of 3.88 per cent, particularly pleases us.

We have found it necessary to do cesarean section for about the same indications, and in like order of frequency, namely, repeat cesarean, disproportion, toxemia, and hemorrhage, etc.

Ethylene anesthesia is chiefly used in our department; local anesthesia is used in cases of toxemia.

I should like to ask Dr. Free first, how often they allow a woman to go into labor, who has had a previous section? Lately, our policy has changed a bit regarding this. If the indication for which the first section was done, does not now prevail,

some of these patients can be delivered safely. Second, what does he mean by vaginal cesarean section at term?

DR. FRED O. PRIEST.—The incidence of sections at the Lying-in Hospital is somewhat higher than that at the Presbyterian Hospital: 4.43 per cent, while ours has been 1.57 per cent. Since 1939, however, our incidence has risen to 3.52 per cent. We attribute much of this increase to the fact that our outpatient department was discontinued in 1940, thereby decreasing our total number of deliveries, while we have continued to draw a considerable number of repeat sections from that group.

Dr. Free reports also a much higher proportion of low cervical sections than we can report. His report is of recent work, while our report goes back to 1930, and our present trend is more and more toward the low cervical operation. Furthermore, we have not classified a case as low cervical even though the incision was chiefly in the lower uterine segment, if the upper portion extended into the lower fundus and was not completely covered by the bladder flap of peritoneum in closing. We could decrease our classical percentage markedly if we called these *Low Fundal*.

I am impressed by the ability of the operators in this report to use the true low cervical technique in such a high percentage of repeat sections—even in the third and fourth sections. They report doing only four classical operations in 194 repeat sections. We have not been able to maintain such a percentage.

Both our maternal mortality and morbidity have been higher than that reported by Dr. Free. On the other hand, we have had only twenty fetal deaths (uncorrected) or 6.8 per cent, while he reports 9.2 per cent.

Our indications for cesarean section and percentage done for each indication correspond closely with those at the Lying-in, except that we have done fewer for cardiac reasons. We have done a comparable number of sterilizations on repeat sections, though a much lower percentage on primary sections.

At least 90 per cent of our operations have been done under ethylene and oxygen. Most of the remainder have been toxemia or cardiac patients and were done under local anesthesia. No patient has been sectioned for cardiac reasons since 1937.

DR. J. P. GREENHILL.—On the supposition that this paper was to contain statistics from the Lying-in Hospital, I jotted down some figures from a paper I wrote fifteen years ago. In 1929, I compiled all the cesarean sections performed at the old Chicago Lying-in Hospital from 1915 to 1929. In 1916, the incidence of cesarean operations was only 0.6 per cent. That figure steadily rose until 1929, when it was 3 per cent, five times as great within a period of fourteen years. The incidence cited by Dr. Free was 4.43 per cent and the incidence given by Dr. Smith for the Evanston Hospital was 3.7 per cent.

Now as to mortality, among the 874 cervical cesarean sections which I analyzed, the death rate was 1.26 per cent. This is practically identical with the Presbyterian Hospital figure but considerably higher than the Chicago Lying-in figure for the last 500 cases.

In my group the indication for cardiac disease was only 3.3 per cent, which was definitely lower than the figure Dr. Free quoted. Only 50 per cent of the patients in my series were in labor, whereas in Dr. Free's group 60 per cent were in labor.

Local anesthesia was used in 58 per cent in my series. In 1929, the last year of my series, 92 per cent of all cesarean sections were done under local infiltration anesthesia.

I compared the death rate after the local cervical cesarean section with that following the classical operation. In the fifteen-year period, practically all the operations were done by six attending men, but most of them were performed by Dr. DeLee. During this fifteen-year period, the death rate in the classical group was three times as high as the mortality for the cervical operation. There were 38 Porro operations without any mortality.



What about the terminology when part of the incision extends into the lower part of the corpus of the uterus? I agree with Dr. Priest that in doing an elective cesarean section, we often have to extend the incision into the upper portion of the uterus a centimeter or more. I still call this a cervical operation. I think we will have difficulty separating these cases from the ones done as typical cervical cesarean sections. In all of these cases, we have the decided advantage of being able to use the bladder peritoneum for complete covering of the uterine incision.

DR. WILLIAM J. DIECKMANN.—The statistics given by Dr. Free include all abdominal hysterotomies of fetuses weighing 400 grams or more. So far as I know, Eastman is the only investigator who has stated that the term cesarean section should be limited to fetuses weighing 1,500 grams or more. The maternal morbidity and mortality for fetuses weighing less than 1,500 grams and especially for those weighing less than 1,000 grams are less than for those weighing more than 2,500 grams.

Some obstetricians are of the opinion that if they have an absolute indication for a cesarean section and the patient dies from the infection, that they are not responsible for it. We believe that if an elective cesarean section is performed and the patient develops sepsis, that the doctor and hospital are responsible irrespective of the indication for the cesarean section. We believe that the maternal mortality from cesarean section should be less than 0.5 per cent.

I have collected almost 2,000 cesarean autopsies, and the principal causes of death were:

Infection and ileus	38 per cent
Embolism	7 per cent
Hemorrhage and shock	30 per cent
Toxemia	19 per cent
Pneumonia	4 per cent
Anesthesia	3 per cent

It is obvious that more than two-thirds of these deaths, that is, those due to infection and most of those due to hemorrhage and shock, as well as those due to anesthesia and a considerable portion of those due to toxemia, are preventable and should not have occurred.

Hospitals should keep a strict account of their results, but they should not refuse to perform operations because it may affect their statistics. For example, one of our cesarean deaths occurred in an eclamptic patient. It was the opinion of the obstetrician in charge, who had been treating the patient medically for almost 24 hours, that the patient was moribund. He felt that the patient should be given a chance of survival, which is occasionally dramatically associated with delivery. This could have been performed by insertion of a bag or by cesarean section. The latter operation was selected because it was felt that time was a factor and a live baby might be obtained. The baby did survive although the mother died from eclampsia and intracranial hemorrhage. Two babies were salvaged by cesarean section on patients with tuberculous meningitis. Obviously, the cesarean statistics were not helped by these cases.

DR. FREE (closing).—The question frequently comes up in relation to a patient who has had a section, then has an intervening labor without a section, and then is again pregnant, whether this patient should be submitted to another section. We have a very definite opinion that all these cases should be sectioned.

In response to the second question, the four cases of vaginal section were included for comparative study with the other 1,000 cases; vaginal hysterectomy was included in the earlier 1,000 cases, and to make our statistics comparable, we included these four vaginal sections. In two cases the fetuses were dead.

## A STUDY OF MATERNAL MORBIDITY\*

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ABOUT 50 per cent of the maternal deaths in the United States are due to infection. Hemorrhage can usually be prevented, and if it occurs, may be readily treated by packing the uterus, and by the use of blood and plasma. Most serious toxemias of pregnancy can be prevented by proper prenatal care, and eclampsia has become rather rare in well-managed obstetric clinics. During the past ten years, there has been a small reduction in the number of maternal deaths from infection; but puerperal sepsis still remains the leading cause of mortality.

The source of puerperal infection may be either endogenous or exogenous. The former is not entirely preventable, but the attending physician can reduce this hazard by bringing his patient to term in the best possible physical condition. It has been shown that the removal of foci of infection will reduce morbidity. The prevention of anemia in the latter weeks of pregnancy is very important.

Bickerstaff<sup>1</sup> at Johns Hopkins recorded the hemoglobin levels of a large group of patients during the last four weeks of pregnancy. He found a marked decline in the incidence of febrility with increasing values of hemoglobin at this stage of pregnancy. During the last few weeks of pregnancy, nothing should be done to disturb the normal vaginal flora, and nothing should enter the vagina. It has been demonstrated that virulent bacteria are seldom found in the vagina or cervix unless they are introduced there.

In this connection Conti<sup>2</sup> demonstrated that a cervix with an erosion has no more organisms than a normal one, and that the morbidity is no higher in patients with erosions. He also demonstrated that the number of streptococci and the respiratory group of bacteria were both increased in cervical cultures during the months when respiratory infections are common.

Exogenous infection may be made less frequent by the use of careful aseptic and antiseptic technique, by the wearing of masks over the nose and mouth, by careful preparation of the patient and by avoiding contacts with attendants who may be carriers of virulent bacteria.

Hemolytic streptococci are the organisms responsible for most of the serious puerperal infections, and they are usually transmitted to the patient from the outside.

In the serious epidemic of deaths<sup>3</sup> from puerperal sepsis at the Sloane Hospital in 1927, it was found that 20 per cent of the nurses, 8 per cent of the doctors, 25 per cent of the students and 8 per cent of the patients had positive cultures of virulent streptococci in their noses and throats. It was also discovered that there was an unusually large number of respiratory infections throughout that part of the country at the time, and that other hospitals reported a higher incidence of puerperal sepsis than was normal.

The use of vaginal instillations of various antiseptics during labor has apparently been a valuable addition to the technique of some institutions.

\*Presented at a meeting of the Chicago Gynecological Society, April 21, 1944.

Mayes<sup>4</sup> reported no maternal deaths in the last 11,000 vaginal deliveries and only one in the last 24,000, since they have used this procedure. The gross morbidity was 7.8 per cent and the corrected morbidity was 3.3 per cent. The gross figure had been 14 per cent before the use of mercurochrome instillations was begun.

In a survey he found that 517 out of 848 Diplomates of the American Board of Obstetrics and Gynecology use vaginal instillations during labor. In his survey of hospitals, 95,890 patients were delivered with only 12 deaths from sepsis as compared with 6 deaths in 13,424 deliveries where this procedure was not used.

Brown<sup>6</sup> reported no maternal deaths from sepsis in patients having cesarean sections, since he has used vaginal instillations. In a study of cervical cultures, he found growths of bacteria in only 4 per cent when using this technique as compared to 44 per cent when it is not used.

I wish to present some statistics from the Evanston Hospital, covering a period of three years, from 1941 to 1944. There has been no important change in the technique used in the labor and delivery rooms for many years. We have not used routine vaginal instillations of antiseptics. It was used by one members of the staff but was later discontinued as there was no appreciable difference in his results. We insist that all attendants cover their noses and mouths, not only in the birth rooms but also on the maternity floor, when examining post-partum patients.

On admission to the labor rooms, patients are shaved and given enemas unless labor is too far advanced. Rectal examinations are used to determine the progress of labor except when an occasional vaginal examination is needed. When this, or any other vaginal manipulation is used, such as rupture of the membranes, the skin around the vulva is painted with an antiseptic solution and mercurochrome is instilled in the vagina with a syringe just before the examination is made. At the time of delivery, the skin is first cleaned with soap and then painted with an antiseptic before the patient is draped. We do not consider the skin as sterile, and maintain a "Hands Off" policy as much as possible.

Ergotrate is given intravenously at the end of the second stage by part of the staff, and intravenously at the end of the third stage of labor by others. It is not used routinely during the puerperium.

Although the maternity department is not housed in a separate building, it is isolated from the rest of the hospital, and the attendants do not have contact with other types of patients.

Almost all of our patients are under our control during the prenatal period and they are from a class which is well nourished, and they have whatever advantages a high economic standard may bring.

During this three-year period, there were 3,457 patients delivered in the hospital. Of these, 176 or 5.09 per cent developed a febrile morbidity. Removing those in whom the fever did not arise from the genital tract, the corrected figure is 3.64 per cent. There was one death in this group; this patient had a severe eclampsia. Postmortem examination showed terminal bronchopneumonia, necrosis of the liver and toxic nephrosis. Comparative statistics from different hospitals are difficult to correlate, as a different standard may be used. Morbidity rates from 6.5 per cent to 25 per cent have been published; a general average being about 10 per cent.

Our basis for morbidity is a temperature of 100.4° F. on any two days after the day of delivery. Temperatures are taken only twice daily unless there is fever. When fever appears, the temperature is taken every four hours. Many patients in this corrected group who had only two days of fever probably had fever from a source outside the genital tract, but unless a definite diagnosis was made they were all put in the puerperal sepsis group.

The number of days of febrility is important in studying maternal morbidity. A fever lasting two or three days is of little consequence and has little effect on the patient's convalescence; whereas, a fever lasting many days means a more serious infection which has probably spread beyond the uterus.

For detailed analysis of these patients I have eliminated those whose fever arose from outside the genital tract, because my object is to try to determine what obstetric procedures or complications cause puerperal sepsis.

This group of 124 patients had an average of 3.7 days with morbid temperatures. There were 52 who had a fever for 2 days, and 32 with fever for three days. Table I shows the total number of days morbidity.

TABLE I. DAYS OF MORBIDITY

Days	2	3	4	5	6	7	8	9	13	14	27
Patients	52	32	13	11	4	4	3	1	1	2	1
124 patients—Average days morbidity—3.7											

The average age of the women in this report was 28 years. About one-half of them were over 30. This corresponds with other reported statistics which show a lower morbidity up to age 30, with a rise above this age. This can be explained by a higher incidence of complications of pregnancy and labor in the older group.

The morbidity declines with advancing parity until a very high parity is reached; this also is caused by a larger number of complications encountered in primipara and again with high parity. Of the patients in this group, about 68 per cent were primiparas, whereas in the total number of patients delivered during the three years about 35 per cent were multiparas.

The average estimated blood loss was 230 cubic centimeters. This appears to be within normal limits, and as we had only four patients with a loss of over 500 cubic centimeters. I believe hemorrhage played a very small part in our morbidity. It has been shown that when blood loss is over 600 c.c., fever appears two to ten times as often.

The average length of labor was 12 hours and ten minutes, which is below average. The average length of labor of the patients with more serious and prolonged morbidity is greater than that of the entire group. This corresponds with the general impression that morbidity increases with the length of labor.

Pre-eclampsia occurred in 15 per cent of our morbid cases. This is about 6 per cent above average figures for the frequency of this complication and suggests that toxemias predispose to infection.

The various types of delivery showing the percentage of morbidity are shown in Table II. As might be expected, the more extensive operations carried with them the highest morbidity. This rate increases directly as the operation nears the uterus. Cesarean sections,



TABLE II. RELATION OF MORBIDITY TO OPERATIONS

	TOTAL CASES	MORBIDITY	
		CASES	PER CENT
Low cervical cesarean section	120	21	17.50
Classical cesarean section	3	2	66.60
Manual rotation	181	11	6.07
Midforceps	86	3	3.48
Low forceps	1,899	57	3.00
Breech extraction	105	4	3.80
Craniotomy	1	1	100.00
Version and extraction	13	0	0.00
Packing of uterus	38	14	36.84
Manual removal of placenta	46	4	9.09
Artificial rupture of membrane for induction	433	10	1.76
Loosening of membrane for induction	36	5	13.88
Cervical repair	194	11	5.67
Total operative	2,226	106	4.76
Spontaneous	1,253	25	3.19

packing the uterus and manual removal of the placenta, carried the highest morbidity rates.

The morbidity in the cases delivered operatively was 4.76 per cent. If the low forceps deliveries are removed from this group, the morbidity for the more difficult operations is 14.98 per cent. The figure of 3 per cent for low forceps compares very favorably with that for spontaneous delivery, which was 3.19 per cent.

Of the patients who had episiotomies or tears, 6.8 per cent had morbid temperatures. In only three of these was any infection of the repair discovered. The patients who had tears or episiotomies and no other operations or complications had only about 1 per cent morbidity, showing that this operation carries a very low morbidity.

In the total series of 3,457 patients, artificial rupture of the membranes for induction of labor was done 433 times or in 12.5 per cent. Loosening of the membranes for induction was done only 36 times. Also the membranes were ruptured after labor was in progress 136 times. This was done to stimulate labors which were not progressing, or just before delivery to remove a membrane which was retarding labor.

In the group of patients who were induced by rupturing of the membranes only 10 or 1.76 per cent developed puerperal infection. Of the patients who had the membranes loosened, 5 or 13.88 per cent developed puerperal sepsis. The insertion of a small sterile instrument into an open cervix is less likely to carry infection up from the lower genital tract than is the insertion of a finger, which is then smeared over the inner surface of the lower uterine segment. In a large portion of our cases, the perforator is passed into the cervix under the guidance of a finger in the rectum.

The frequency of induction of labor by this method may seem rather high but it is done only when the cervix is effaced and partly dilated, and the presenting part has entered the pelvis. As the figures show, it does not increase morbidity and we have had no increase in fetal mortality as a result of the procedure.

In Table III, the percentage of morbidity is shown by months. In general, it shows no regular seasonal variation. However, months when respiratory infections are common more often show a higher febrile morbidity. This has been borne out by others, such as Watson, at the Sloane Hospital.

TABLE III. SEASONAL VARIATION OF MORBIDITY

JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
5.07	7.87	7.53	3.80	2.95	2.83	5.01	5.32	7.09	4.79	4.14	4.79

The incidence of morbidity in the patients cared for by individual members of the staff was studied. No notable difference was found.

The prevention of puerperal sepsis is chiefly the responsibility of the physician. Certainly, a large majority of these infections are preventable. Most modern and well-managed obstetric clinics have reduced their morbidity, but there is still room for improvement. Patients are safer in hospitals than at home. At Johns Hopkins, the morbidity for women delivered at home was twice that of hospital patients. In the United States only 15 per cent of fatal puerperal infections developed in the hospitals.

The care of the patient in labor is probably the most important factor in lowering morbidity. Attention to details in aseptic and antiseptic technique is most essential and must be followed, not only in the delivery room but until the patient leaves the hospital. Various additions to the usual technique, such as vaginal instillations, are no doubt of value as has been shown by several authors, but they are not essential to good results.

It has been clearly demonstrated many times that major obstetric operations carry a higher morbidity. The unnecessary use of these procedures is to be condemned. Trauma in any form definitely increases the likelihood of infection.

The proper use of sedatives and the administration of nourishment during long labors will do much to lessen the exhaustion of the patients, and help bring them to delivery in the best possible general condition.

It has been suggested that when a uterus must be packed, the gauze should be impregnated with sulfanilamide; this supposedly acts as a prophylactic due to its bacteriostatic action. We have had no experience with this technique, but do use 0.5 per cent cresol gauze.

The value of the routine use of ergot in the puerperium to lower morbidity is not universally accepted. It has been argued that it may cause the spread of infection originally confined to the uterus by stimulating strong contractions. Others contend that keeping the uterus well contracted limits the spread of infection.

Since the introduction of the sulfonamides, the fear of puerperal infection has been somewhat lessened, and with good reason. The prompt and judicious administration of these drugs, when indicated, is of tremendous value.

At the onset of fever, cultures from the upper vagina or cervix should be made and examined within 24 hours, so that proper therapy may be used. Sulfanilamide is most effective against hemolytic streptococci, and sulfathiazole or sulfadiazine are best used for other types of infections. Supportive treatment with blood transfusions, proper diet and any measure which may improve the patient's general condition, must not be overlooked.

While all the methods of antiseptics and treatment of infection mentioned above have done much to lower maternal morbidity and mortality, proper prenatal care and skillful handling of the woman in labor are of prime importance. Too much reliance on drugs and antiseptics breeds contempt for careful obstetric technique and sound management of the patient in labor.

### Summary

1. Infection is still the leading cause of maternal deaths in the United States.

2. The source of puerperal infection may be either endogenous or exogenous.

3. Much can be done to lower the incidence of puerperal sepsis by proper preparation of the patient in labor, and by the careful handling of her labor.

4. Three thousand, four hundred and fifty-seven patients were delivered at the Evanston Hospital from 1941 to 1944. The gross maternal morbidity was 5.09 per cent and the corrected rate was 3.64 per cent.

5. A summary of the routine used in the maternity department of the Evanston Hospital is presented.

6. The patients with puerperal sepsis are analyzed in detail. Those who had undergone major obstetric operations carried the highest morbidity rates. Those who were delivered with low forceps had a lower morbidity rate than the patients who were delivered spontaneously.

7. Artificial rupture of the membranes for the induction of labor caused no increase in febrility.

8. There was very little seasonal variation in the morbidity rate except for some increase during the months when upper respiratory infections were more common.

9. The prevention of puerperal sepsis is chiefly the responsibility of the attending physician.

10. The more recent additions to the treatment of puerperal sepsis are briefly discussed.

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### Discussion

DR. IRVING F. STEIN.—As Dr. Cummings has said, the last decade has shown little improvement in the mortality from sepsis, which is still the leading cause of maternal deaths. All of the efforts made to improve delivery technique have failed to provide an adequate prophylaxis.

Every attempt should be made to exclude carriers of virulent streptococci from birth room and nursery and routine examination for carriers should be made, as some of the most highly fatal epidemics have been traced to these sources. However, the parturient herself may enter the delivery room having an acute upper respiratory infection, thus presenting a potential menace to the maternity service as a whole.

The use of antiseptics in the birth canal has doubtlessly reduced morbidity in some clinics. However, Dr. Cummings reports a morbidity of 3.65 per cent among 3,457 patients in three years at the Evanston Hospital where this technique was not used as compared with 3.3 per cent reported by Mayes. Obviously, other factors are prominently involved. At Michael Reese Hospital, we found no essential difference in morbidity when using various antiseptic techniques such as tr. iodine, mercurochrome, tr. metaphen than when green soap and sterile water were

employed, so for several years we have completely abandoned the routine use of antiseptic preparations. Only sterile water is used during delivery. In two years we had 4,309 deliveries with a morbidity in 139 patients or 3.12 per cent.

The author's report of 10 of 433 who developed sepsis after puncture for induction, and 5 of 36 who were septic after loosening of membranes should be noted. Only green soap and sterile water are used in preparation for puncturing the membranes at Michael Reese Hospital. I personally do not subscribe to the routine rupture of membranes for the induction of labor, and, in fact, rarely induce labor at all. There are some obstetricians who do practice this procedure, however, with reported good results. For the simple puncture of membranes, I wish again to recommend the simple "midwife's fingernail" which I presented to this Society in 1935, and which we have used with great satisfaction for ten years. The use of the finger in the rectum as a guide for a vaginal operation, be it merely puncture of membranes, seems to me to be a reversion to the practice of former times when the doctor was not permitted to view the genitals but was required to examine women sight unseen.

Responsibility for the prevention of infection, insofar as is possible, rests unequivocally with the physician, and to this end, attention to careful aseptic delivery room technique is most important. In addition to the usually accepted measures, should we not consider the value of the sulfa drugs used on uterine packs, and in the uterine cavity and the peritoneal cavity during cesarean section as additional prophylaxis? In gynecologic operative work, we have used sulfathiazole gauze as drains with satisfactory results and this might well be adapted to obstetric operative technique.

The advent of sulfa therapy and the prospects of even greater and more spectacular cures from penicillin, gramacidin and perhaps as yet undiscovered preparations bid fair to decrease greatly the mortality and morbidity in obstetrics during the next decade. As Dr. Cummings warns, however, we must not allow careless habits to creep into the delivery room because of the curative value of sulfa drugs.

DR. J. E. FITZGERALD.—So-called maternal morbidity varies from the low figure noted by the author to upward of 20 per cent. This variation is due less to the difference in sick postpartum patients in good maternity services than to the frequency with which temperatures are recorded and to the type of cases corrected out from the gross number of febrile patients. I suspect that Dr. Cummings would have found more febrile reactions if temperatures had been recorded oftener than twice daily. We can, however, all agree on the main point of his essay, namely, that postpartum fever is more common after long and complicated labors, and in patients who are physically below par when they go into labor.

Maternal morbidity is an ugly term to describe a perfectly well patient who has two temperature readings of 100.4° F. in ten days. It is misleading to the public and the profession alike, because morbidity is by common usage associated with forms of illness more serious than the vast majority of these patients present.

The importance of an afebrile postpartum period and the reduction of true postpartum sepsis are not to be underestimated, but I believe we would get a better general picture of the postpartum period and more accurate statistics of postpartum fever if we could replace the term maternal morbidity by one more accurate and less ominous.

DR. CHARLES NEWBERGER.—During the year 1943, in hospitals of the state of Illinois, 285 mothers died, a mortality rate of 2.1 per 1,000 births.

The definition of the term morbidity is a temperature of 100.4° F. on any two occasions, excluding the first twenty-four hours, provided the temperature is taken



four times daily. This last-mentioned requirement must be observed. Many hospitals failed in giving adequate consideration to this matter. There were instances of hospitals reporting over 1,000 births with no maternal morbidity. One Chicago hospital reported 210 births in one month with no morbidity, but also indicated a maternal death from puerperal sepsis.

My remarks are intended to be a plea to physicians to see that the records are properly kept. Patients with toxemia or with hemorrhage are more apt to be reported as such than the patient who has temperature post partum. In an institution like the Evanston Hospital, I presume these records are kept more accurately and the results mean something, but in the average hospital that is not true.

In reply to the point that Dr. Cummings made about sepsis taking first rank in maternal mortality, I would like to point out that the survey made for 1943, of all obstetric deaths in Illinois showed that toxemia was responsible for 31.2 per cent, hemorrhage for 14.2 per cent and infection was the assigned cause in 12.6 per cent.

DR. W. C. DANFORTH.—The morbidity reported from the Evanston Hospital we thought might be questioned as being rather lower than it should be. I was interested to see, however, in a report that I received from Springfield the other day, that hospitals in this state with 1,000 or more births per year have a comparable morbidity. Hospitals that have that many births are the better run institutions, so that I think our morbidity is not out of line.

There has been a good deal of discussion about vaginal antiseptics and I very definitely feel that these are of little use. I think even that the use of antiseptics is contraindicated. The chief thing to do with the vagina of a pregnant woman, or a woman in labor is to leave it alone. Our technique, except for one short period when a few attempts were made to compare some of the different antiseptics, has been to use none. The use of an antiseptic solution on the skin I feel is more of a gesture than anything else. Thorough cleansing with soap and water is all we need.

As to puncture of the membranes for the induction of labor, I have never agreed that rupture of the membranes with an undilated cervix is a correct procedure, so rupture of the membranes with us has been confined to women with effacement and some opening of the cervix. We merely rupture the membranes by some simple means without any dilatation of the cervical canal. When one induces labor by introducing the finger in the cervix and swinging it around rupturing the membranes, it seems the danger of infection is greater. The flow of fluid afterward has some value in doing away with any introduction of infection. When we wish to rupture the membranes when there is 5 or 6 cm. dilatation, we do it by the use of a long narrow perforator.

DR. CUMMINGS (closing).—As Dr. Fitzgerald mentioned, taking temperatures only twice daily means we no doubt miss a certain number of infections, but I do not suppose we miss any that are serious. If the patient does develop a fever, we take the temperature every four hours. It was shown that most of the infections that developed had at least two or three days of fever.

Maternal morbidity figures as well as other statistics are hard to compare because hospitals use different standards. When we study the statistics from the State of Illinois, we find the morbidity rate is higher than ours, but apparently the Illinois figures are better than the country as a whole.

## HIRSUTISM IN PREGNANCY

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A CONDITION commonly confronting the physician is that of excessive facial hair growth. Hirsute women often consider themselves ostracized not only by society, but by their husbands and families as well. Psychoneuroses may be precipitated or aggravated by this condition, yet few patients leave the gynecologist with their affliction relieved.

Multiple factors no doubt operate to produce this condition, yet investigation has proceeded largely along endocrine lines because certain hormonal abnormalities are commonly associated with hirsutism. Probably the commonest type of hirsute problem is the woman who develops facial hair growth at or after the menopause. The menarche may herald its onset. Amenorrhea often precedes or accompanies the onset of varying degrees of hirsutism. The administration of large doses of male sex hormones will produce this condition. Cushing's syndrome, a clinical term applied to cases with adrenal cortical hyperplasia, adrenal cortical tumors or thymus tumors is usually accompanied by excessive hair growth. Cushing's disease refers to a similar clinical picture, which has as its probable origin a basophilic adenoma of the pituitary. When the pathology can be recognized and corrected, improvement is to be expected. In the largest group of hirsutes, however, the cause cannot be found and the patient is finally referred to the dermatologist for depilatory treatment.

The condition to be discussed in this paper is not often of sufficient degree to cause concern either to patient or physician. This is evidenced by the paucity of reports in the literature.

While a number of authors<sup>1-4</sup> state that hirsutism commonly occurs in pregnancy, to this writer's knowledge, there are only five case reports in the literature. Slocum<sup>5</sup> reported a patient who with each of three successive pregnancies developed marked facial hair growth. This fell out each time four to six months post partum. Hegar<sup>6</sup> mentioned a case, but did not state whether the hair dropped out post partum. Hertzel<sup>7</sup> and Jellinghaus<sup>8</sup> had similar cases. McCarthy<sup>9</sup> had a 36-year-old woman who developed this condition with each of three pregnancies. She noted a marked diminution in excess hair five weeks post partum.

Other authors have found a tendency toward alopecia during pregnancy or the puerperium. Ochs<sup>10</sup> had a patient who with each of two pregnancies developed alopecia areata, only to regain her hair one month post partum each time. Becket<sup>11</sup> noted alopecia totalis following pregnancy in a 33-year-old woman. He makes no mention of the hair growing back.

Trotter<sup>12</sup> found no difference in rate of hair growth in seven women studied during pregnancy.

In experimental animals similar conflicting findings have been observed. Halban<sup>13</sup> shaved the abdomens of pregnant and nonpregnant rabbits and found that hair growth was well established in the pregnant

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animals in four to five days, while in the nonpregnant one to two weeks was required. Dawson<sup>14</sup> noted a definite decrease in the rate of hair growth during pregnancy in the guinea pig.

It appears, then, that in some species hair growth seems to be stimulated by pregnancy, while in others it is depressed. Human beings apparently may show stimulation, depression or no change in rate of hair growth during pregnancy.

### Report of Cases

CASE 1.—(The author is grateful to Dr. A. Dale Kirk, Flint, Mich., for permission to report this case.)<sup>15</sup>



Fig. 1.

R. P., a 27-year-old primigravida, reported first for prenatal care July 3, 1936. Her last menstrual period had been May 29, 1936. On August 10, she reported excessive growth of hair on face, arms and legs and over her back. The growth was especially heavy on the sides of the face and under the ears where it appeared in small whorls. (Fig. 1.)

Menstrual history was normal. The patient had been known to have a low blood pressure for a number of years, and three years before, her basal metabolic rate had been low.

Physical examination was essentially negative save for the pregnancy and the hirsutism.

Basal metabolic rate was checked and found to be  $-11$ . Scout film of the abdomen failed to disclose any shadows suggesting adrenal tumors.

Roentgenogram of the sella turcica was found to be normal. Her eye grounds showed no abnormal findings.

The hair continued to grow throughout the pregnancy. On March 12, 1937, she spontaneously delivered a normal male infant.

About eight weeks post partum, she had a menstrual period. Shortly thereafter while taking a bath, she noted that on rubbing the skin surface with a rough turkish towel the hair could be rubbed off. She completed the hair removal that afternoon and her hirsutism disappeared. (Fig. 2.)



Fig. 2.

One and one-half years later, she repeated precisely the same performance. The patient has been seen on numerous occasions since then, and she is free from excess hair and there are no masculine characteristics.

CASE 2.—N. K., a 28-year-old primigravida, was first seen in the Department of Obstetrics and Gynecology of the University of Michigan Hospital in February, 1943. She stated that her last menstrual period was November 8, 1942, and that at about Christmas time she noted the rapid appearance of soft, luxuriant hair growth over the entire body, mostly on the face. (Fig. 3.)

Menstrual history had been perfectly normal. Neither she nor any of her relations had noted deepening of the voice or change in body habitus. Past medical history was noncontributory. No one in her family had suffered from a like condition.



Physical examination showed a normally developed woman with no masculinizing features other than the facial hirsutism, largely confined to the eyebrows and cheeks. A slight, but definite increase in growth had been noted on the upper lip and chin by the patient. There was also generalized hirsutism, but being blond it was not photogenic. One interesting feature is that the normal female pubic hair distribution remained unchanged. No purplish striae were noted. No abdominal tumors were palpable other than an apparently normal pregnant uterus. Pelvic examination was compatible with a three months' pregnancy. A sense of resistance was felt in the left adnexa. No hypertrophy of the clitoris was noted.

None of the roentgenograms showed osteoporosis. Scout film of the abdomen showed no abnormal calcification, nor any tumor masses in the upper abdomen. Chest and skull films were negative.



Fig. 3.

Blood pressure ranged from 130/85 to 140/88, hemoglobin from 56 per cent to 70 per cent and W.B.C. from 4,250 to 16,540. The only red cell count during the pregnancy was 2,850,000, taken when the hemoglobin was 56 per cent.

Urinary estrogens of 2.5 mg./24 hours were compatible with four months of pregnancy. The 17-ketosteroid levels of 12.0 and 8.2 mg./24 hours were definitely higher than our normal pregnancy range of 3 to 6.5 mg./24 hours. Aschheim-Zondek tests were positive with undiluted urine but negative with dilutions of 1:50 and 1:100.

Salt and water balance tests were considered as a means of estimating the degree of adrenal cortical activity. Due to the fact that salt and water balance in normal pregnancy is disturbed, it was felt that interpretation of such tests would be both difficult and unreliable in this case at the present state of our knowledge.

Perirenal air injection of the renal capsule to outline the adrenals was not attempted because of the very real risk in our experience of air emboli.

Finally, as a diagnostic measure, exploratory laparotomy was performed. This was elected for the following reasons: (1) The essentially negative physical findings save for the hirsutism and the resistance in the left adnexal region. (2) The elevated 17-ketosteroid levels suggested possible adrenal or ovarian pathology. (3) The feeling that if a possible hair growth producing tumor were allowed to grow unchecked, irreparable damage might result. (4) It was felt that if on exploratory laparotomy no tumor was found, the family could be dissuaded from considering termination of the pregnancy.

At the time of exploratory laparotomy, the uterus was the size of a four and one-half months' pregnancy. Several implants on otherwise healthy appearing ovaries were interpreted both grossly and microscopically as decidual implants. The adrenal glands were palpably normal both in size and consistency. The pregnancy was allowed to progress to a normal termination. The patient delivered a 7¼-pound female infant on August 19, 1943. The infant has been followed regularly and is normal in every respect.



Fig. 4.

During the puerperium, the patient was followed closely and by November, 1943, the hair had definitely decreased. By January, 1944, all abnormal hair growth on the face and body had disappeared. (Fig. 4.) On November 2, 1943, the 17-ketosteroids were 3.4 mg./24 hours. The normal nonpregnant range in our series is 1.5 to 8.5 with an average of 5.3 mg./24 hours.

#### Discussion

In the differential diagnosis of this condition, we considered the causes of Cushing's syndrome, arrhenoblastoma, teratoma of the ovary,

an abnormally functioning placenta, and some abnormality of the fetus. The influence of the generalized hyperemia associated with pregnancy on the hair follicles of a susceptible individual was also considered as a possible cause. Our investigations failed to substantiate any of these possibilities. There are no published endocrine studies on this type of patient to the author's knowledge. The consensus of opinion among those who have studied these cases is that the hirsutism had its origin in the maternal adrenal cortex.

What evidence do we have for this belief? (1) The suggestively high 17-ketosteroid levels during pregnancy and the normal postpartum level in Case 2. These substances known to be associated with hair growth are normally formed in the adrenal cortex rather than the ovaries since castration does not alter the levels while adrenal atrophy as in Addison's disease causes a marked decrease. (2) Ovarian inspection and biopsy failed to reveal any possible etiology. (3) In experimental animals, the adrenal cortex is stimulated to increased size presumably by high levels of the hormones of pregnancy. This has also been demonstrated by administration of large doses of estrogens.

Certain questions must be answered before we can settle on the maternal adrenal cortex as the responsible factor. (1) Can the placenta, known to produce the steroid hormones, estrogens and progesterone, also under certain conditions elaborate a hair growth producing 17-ketosteroid? (2) Does inspection, palpation and random biopsy rule out the ovaries as etiologic factors? (3) Can some fetal factor influence maternal hair growth? (4) Are hair follicles in the susceptible individual stimulated to growth by the hyperemia of pregnancy?

### Conclusions

Hirsutism of marked degree is rare during pregnancy. These cases should be studied thoroughly to rule out possible concomitant hair growth producing neoplasms. In the absence of definitely demonstrable neoplasms by clinical, laboratory or x-ray studies exploratory laparotomy offers little. The patient should be assured that the hirsutism will in all likelihood disappear post partum, but will probably return with subsequent pregnancies. There is no indication here for the termination of pregnancy.

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## HYSTEROSALPINGOGRAPHY AS A DIAGNOSTIC AID IN CERTAIN TYPES OF RUPTURED UTERI

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**R**UPTURE of the uterus was first described by Guillemeau and since his time, numerous accounts of this serious obstetric accident have been recorded. There is no way of accurately ascertaining the number of cases of ruptured uteri or its incidence. Unquestionably, many deaths from ruptured uteri have gone unrecognized and the cause of death has been incorrectly given as "childbirth," postpartum hemorrhage, etc.

There is no great difficulty in recognizing the classical picture of ruptured uterus in pregnancy. There is usually a history of a uterine scar or intrauterine manipulation (version), sudden severe tearing pain, marked shock and prostration. In these cases the blood bank, plasma, and surgery can quickly answer the need for life-saving action. However, not all cases of uterine rupture present this picture, for the symptoms may be quite mild. These "quiet" cases can be a real diagnostic problem. This is a report of such a case, in which the use of hysterosalpingography aided greatly in the diagnosis. We feel that this diagnostic aid is a fairly safe procedure to use in such cases, and the information obtained quite valuable. For this reason, we are reporting the following case.

### Case Report

This was the patient's second pregnancy. Her first pregnancy five years previously had been complicated at term by a prolapsed cord. A classical cesarean section was done, and a live baby obtained. Her post-operative course was quite stormy, peritonitis developed and only after several transfusions and a prolonged period of hospitalization did she survive.

The prenatal course of her second pregnancy was uncomplicated until the beginning of the ninth month. At this time, she began to have a moderately severe backache and was advised to go to the hospital. She arrived there about four hours later, and just before admission, the pain disappeared. At that time, her blood pressure, pulse and respirations were all within normal limits and her general physical condition excellent. That evening she stated that she no longer felt the baby move, and no fetal heart was audible. Stilbestrol was given by mouth to sensitize the uterus with the expectation that labor would start spontaneously at any time, and the dead fetus be expelled. A flat plate taken on the fourth day showed overlapping of the fetal skull bones. As labor had not started by this time, it was decided to do a sterile vaginal examination. Little had been ascertained by rectal or abdominal examination because of obesity.

The vaginal examination revealed a mass which was thought to be the uterus, separate from the pregnancy. There was some tenderness in the left lower quadrant. At this time the possibility of the fetus being outside the uterus was first thought of, but we hesitated to do a laparotomy until we could be sure the pregnancy was extrauterine and that we were not doing a cesarean section for a dead baby.





Fig. 1.—Two and one-half cubic centimeters lipiodol. Uterine cavity well outlined.



Fig. 2.—Five cubic centimeters lipiodol. Dye beginning to pass out tear in left side of uterus.

It was then we decided to make a hysterosalpingogram following the technique of Hyams. The accompanying pictures taken after the fractional administration of lipiodol show the uterine cavity outlined and the dye escaping out the tear in the left side of the uterus. The x-ray diagnosis was extrauterine pregnancy.



Fig. 3.—Seven and one-half cubic centimeters lipiodol. Dye free in abdominal cavity, some dye going into right tube.

Laparotomy was done the following day. No blood was found in the peritoneal cavity, the escaping fetus having acted as an efficient tamponade. There was no sign of any tissue reaction to the lipiodol. The fetus, amniotic sac and placenta were lying free in the abdominal cavity, the omentum being only slightly adherent to the placenta. After these were removed, inspection of the uterus showed it to be undergoing involution. There was a tear, evidently through the old scar in the left side of the uterus extending from just below the insertion of the tube down into the left side of the cervix. A supravaginal hysterectomy was done and one gram of sulfanilamide powder placed in the peritoneal cavity. The patient's postoperative course was uneventful.



Fig. 4.—Ten cubic centimeters lipiodol. Dye free in abdominal cavity. Uterine body outlined, dye in right tube.

### Conclusions

1. Rupture of the uterus can occasionally be almost symptomless.
2. Probably there is a much higher incidence of rupture through classical scars, the literature showing only a few through low cervical scars.
3. There is a weakening effect of infection on proper scar formation.
4. Fractional injection of a dye (lipiodol) can give aid in the diagnosis of these cases.

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## BILATERAL, MULTILOCULAR, PSEUDOMUCINOUS CYSTS OF OVARIES NECESSITATING CESAREAN SECTION

A. HERBERT KANTER, M.D., COLUMBUS, OHIO

**M**RS. L. B., aged 26, a white woman, called at my office on March 8, 1944, complaining of severe pain throughout the entire abdomen and back, and extending down both thighs, but more marked in the right and left iliac regions.

The patient had a great deal of difficulty in sitting down and also had difficulty in breathing.

A hypodermic of morphine sulfate had to be administered to relieve pain.

The first symptom occurred October 5, 1943, which was severe abdominal pain. The patient was ordered to the hospital by her physician, who felt that she was about six months pregnant, judging by the size of the abdomen, and that she was going into premature labor. She was symptomatically treated.

She told her physician that it was impossible that she should be six months pregnant, due to the fact that she had last menstruated August 10, 1943.

After six days' hospitalization, she was again seized with severe abdominal pain and vaginal bleeding. She called another physician, who sent her into the hospital. Because of the size of the abdomen, which had the appearance of an eight months' pregnancy, an attempt was made to induce labor, but when the above symptoms stopped, she was sent home.

The patient began menstruating at the age of nine. Periods were at regular intervals of 28 days, lasting 4 days. The amount of flow was moderate. She last menstruated on August 10, 1943.

The patient was married at the age of 17, and has been married eight years. She is a para iv. At the age of 19, she had her first child; at the age of 21, a second; and at the age of 23, her third. They were all spontaneous deliveries.

My examination revealed a well-developed and fairly well-nourished individual; six feet three inches in height, weighing 141 pounds, with fair skin and light hair.

The physical examination was entirely negative, except that I found the uterus extending up to the ensiform cartilage.

The individual had a marked fullness and protrusion of both the right and left lower abdominal regions. The right side was more marked and protruded considerably. It formed a round mass about the size of a child's head. The masses in these regions seemed fixed, but the uterus was freely movable from below.

The chest was normal throughout, the breasts were well developed, and rather soft. The heart and lungs were negative. The blood pressure was 126/75.

The abdomen was rather long, and the pelvis wide and broad. The skin of the abdomen was very tense and glistening, due to the excessive stretching. There was marked bulging and fullness in the right and left pelvis, caused by bilateral masses which were freely movable.

No fetal heart was heard. The fetus was not palpable below the umbilicus but was palpable above. There was an area of dullness on percussion in the lower two-thirds of the abdomen. The rectal examination revealed nothing. On vaginal examination, the perineum was slightly relaxed and a small cystocele was present. The cervix was long and of firm consistency. There was no ballottement, as the masses on both the right and the left side seemed to be crowding the uterus and pushing it posteriorly and upward.

The urine was negative. Blood coagulation time: 3 minutes. Erythrocytes: 5,800,300. Leucocytes: 8,200. Large lymphocytes: 58 per cent. Large mononuclears: 2 per cent. Polynuclear: 2 per cent. Neutrophiles: 40 per cent. Eosinophiles: 2 per cent. Wassermann and Kahn tests were negative. X-ray, taken of both abdomen and pelvis, revealed a fairly large child, vertex presentation. The pelvis was normal and ample.

The termination of the patient's pregnancy was calculated as between May 15 and 20, 1944. But on May 5, due to increased pain and enlargement of the abdomen, I sent the patient to the hospital where she was prepared for operation. A spinal anesthetic was administered. Following this, the patient was given  $\frac{1}{320}$  grain of ergotrate, intramuscularly. A midline incision was made above the umbilicus and extending down to the symphysis. The abdomen was opened in the usual manner.

Through a longitudinal incision into the uterus, which was slightly contracted, a podalic extraction was performed. The child, a male, weighed 9 pounds, 7 ounces. Another  $\frac{1}{320}$  grain of ergotrate was injected into the uterus, and the placenta removed manually. The uterus was closed in the normal manner.

Examination of the right pelvis disclosed a large cystic ovary on a twisted pedicle. The blood vessels were much enlarged and marked varicosities present. Both ovarian cyst and tube were removed.

The left side also revealed a large ovarian cyst, which was removed.

The pathologic findings were the following: The left tube was somewhat stretched over a cystic ovary and measured 12 cm. in length by 6 mm. in diameter. It was smooth, straight, somewhat congested, and apparently patent. The ovary measured 15 by 13 by 9 centimeters. The external surface was smooth and round, slightly injected, and slightly hyperemic. On section, the ovary was found to be cystic and to consist of two cavities, each filled with thick pseudomucinous material, and one containing flakes of blood pigment. The inner surfaces of the thin walls were smooth. The right tube was stretched over an ovarian cyst and measured 12 cm. by 5 millimeters. It was similar in appearance to the one first described. The ovary measured 22 by 15 by 5 centimeters. The external surface was irregular, and presented injected vessels. On section, this ovary likewise was found to be cystic and to contain three cavities, each filled with clear, pseudomucinous material. The inner surfaces were smooth and the walls were thin.

*Microscopic.*—Sections from each ovary presented cysts lined with a single layer of tall columnar, mucous-secreting epithelial cells. The cyst wall was composed of collagenous connective tissue stroma and

some ovarian stroma. There was no evidence of anaplasia, invasion or malignancy. Sections of tubes showed them to be somewhat compressed, with empty lumina. The plicae were slightly edematous, and showed slight lymphocytic infiltration.

This patient had never complained of any pain or noticed any enlargement, and the pregnancy seemed to have stimulated the growth of these ovarian cysts. No doubt, had the rate of growth been more rapid, the pregnancy would have been terminated much earlier.

Had she been permitted to deliver by the vaginal route, it is very evident that there would have been a rupture of either of the ovarian cysts, causing internal hemorrhage due to the increased size of the blood vessels and resulting in the death of the patient.

The mother and child had an uneventful recovery, and left the hospital on the tenth day.

558 EAST LIVINGSTONE AVENUE

## **X-RAY STUDIES IN HYSTEROSALPINGOGRAPHY, USING A NEW CANNULA**

A. P. HUDGINS, M.D., CHARLESTON, W. VA.

**T**HE use of a new cannula, devised by the writer, for hysterosalpingography, requires slightly different x-ray interpretation when the films are read.

This new, indwelling, self-retained, valve cannula can be inserted in the physician's office, the opaque medium injected and the patient allowed to walk to the x-ray room for the film. She then returns for the removal of the cannula and the procedure is complete.

The Colvin, screw-type cannula has been modified by the author by inserting a valve device, and by making the handle detachable. The valve maintains intrauterine pressure and the removable handle makes the examination an ambulatory office procedure. (Fig. 1.) The opaque medium is injected with a regular Luer-type syringe; the tip fitting into the large end of the cannula after removal of the handle.

The use of this cannula has been found to simplify the procedure of hysterosalpingography and it is hoped that wider use will be made of this more complete and detailed method in sterility investigation.

### **Technique of Insertion of the Cannula**

There are a few modifications of the routine procedure which may be helpful to note. The patient is put in the usual stirrup position; a bivalve speculum inserted and sterile preparation of the vagina and cervix is carried out. The cervix is then sounded with a regular number 13, curved cervical dilator. The special indwelling, retained cannula-with-valve is then inserted by clockwise rotation. When it has been inserted as far as possible, so that it becomes firmly fixed in the cervix, the handle is removed and about 6 c.c. of the warmed opaque medium\* is injected. The syringe is detached and the cannula is given one more turn to make sure that it is securely held within the cervix. The vagina should be sponged out to remove any of the opaque medium which may have leaked out into the vagina and which may cause confusing shadows. A regular tampon, with string attached, is left in the vaginal vault to absorb any remaining opaque medium. Instructions are given that this tampon is to be removed before the flat plate is taken. The patient is then instructed to be up and about, and a note is written that the plate is not to be taken for at least 30 minutes after injection has been completed. The purpose of this interval is, of course, to allow the medium to be worked out into the tubes by the muscular contractions of the uterus. If enough time elapses, only one plate will be necessary, thus obviating the necessity of the additional time-consuming procedure of the two-hour and the 24-hour plates.

During the early part of the work, the writer advised the use of the vibrator, applied to the abdomen, to make sure that the medium was ex-

\*Iodochloral (Searle) employed.



pelled and forced out of the tubes, unless obstruction was present. The use of this vibrator, however, has been found to be rarely necessary. The 30-minute time interval, allowing the patient to be up and about, usually accomplishes the same result.

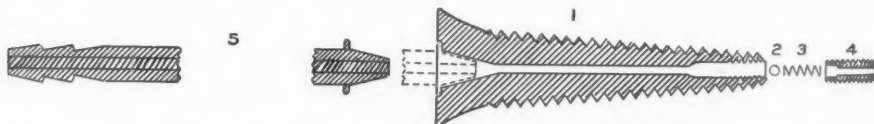


Fig. 1.—Improved cervical cannula. 1. Cannula. 2. Ball valve. 3. Valve spring. 4. Valve plug. 5. Stem.

### Interpretation of Plates

With this method, using the new cannula, one plate is usually all that is required in the investigation for tubular patency. With the old method, when the picture was taken within a few minutes following the injection of the medium into the uterus (and with the patient still in the recumbent position), the uterus and a complete outline of the tubes—with, perhaps, drops free in the peritoneal cavity—were usually clearly seen. Using the new cannula, however, if the tubes are still filled well after the above-mentioned time interval, it has generally proved to be an indication that there is some obstruction. (Figs. 2 and 3.) It has been found that the unobstructed, freely movable tube does not retain the fluid for 30 minutes when the patient is up and about. (Case 1, Fig. 2.)

Gravity, the uterine and tubular contractions, and intra-abdominal pressure are all factors concerned with expelling the medium from the tubes.

A small opening would, naturally, allow a proportionate amount of the material to escape. The interpretation of the single plate, then, is more or less a combination between the first and the second plates (immediate and 24-hour plates) when using the old method. The opaque medium should be chiefly in the uterus and in the peritoneal cavity if the interpretation is to be made of completely unobstructed tubes. There may be a film-like outline, but not a full-size tube structure.

### Therapy

As can be readily seen, this cannula may be retained over a period of time: not only the 30 minutes required for the x-ray procedure, but for 12 to 24 hours, or more, thus stimulating gentle, rhythmic muscular contractions of the uterus in an effort to open up an obstruction of the tubes. In this way, the special cannula can be used not only for diagnostic purposes, but also as an improved method in the effort to open obstructed tubes.

This procedure, utilizing the gentle, continuous, rhythmic, muscular contractions of the uterus over a period of time, has proved to be much more satisfactory than the old method by which pressure was increased suddenly—accompanied by pain, muscular contraction, spasm—and consequent resistance on the part of the patient. The first spasm, or muscular contraction, which comes with the initial discomfort of the injection, gradually subsides and the continued gentle (but forceful) uterine pressure appears to accomplish (over a period of time, after relaxation,

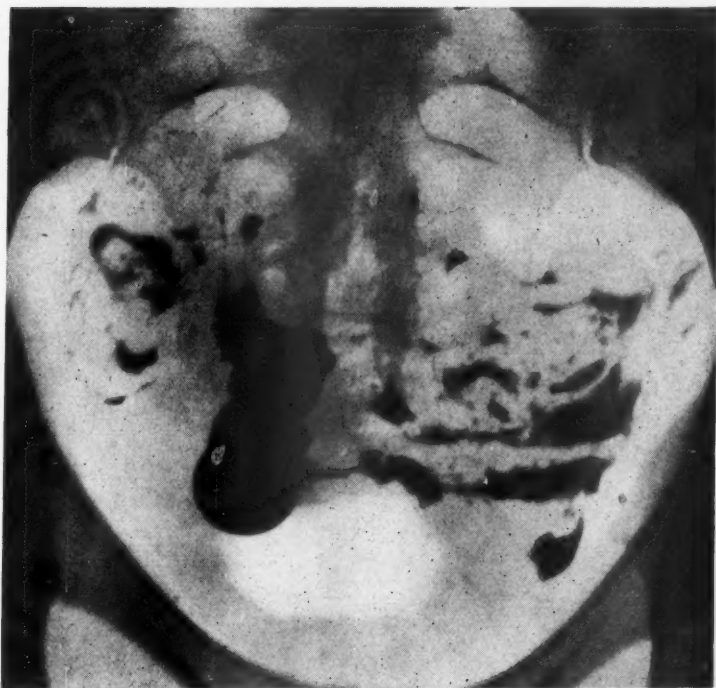


Fig. 2.—Case 1. Cannula retained, with valve. After 30 minutes, vibrator not used. Uterus outlined. No medium in tubes but free complete spill, showing tubal patency, no pathology.

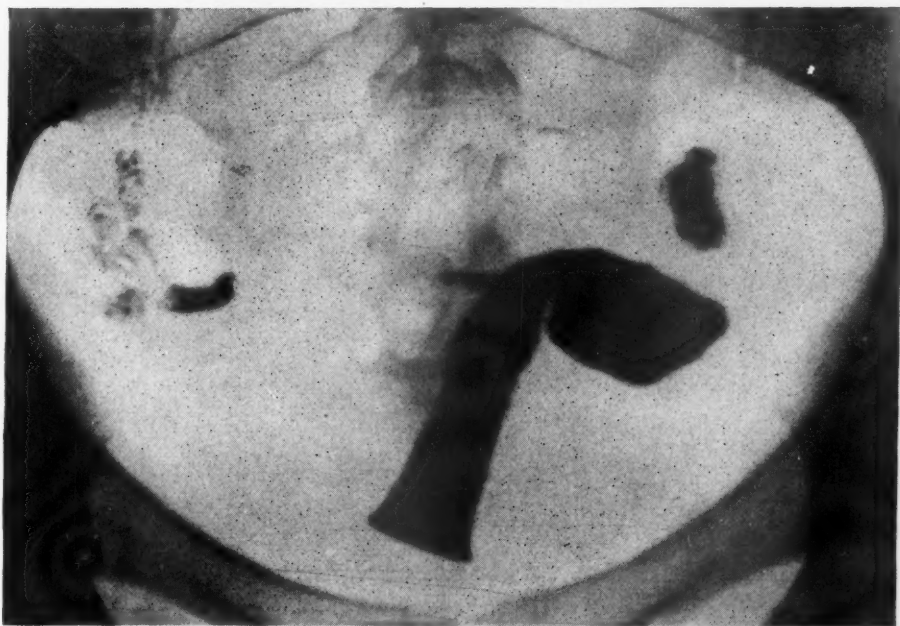


Fig. 3.—Case 2. After two hours, showing medium outlining uterus, small amount at ends of tubes, free in peritoneal cavity. Tubes found closed in several previous hysterosalpingograms.

and after the initial "cramps" have subsided) what is not accomplished by short periods of more artificial, jerky, sudden injection pressure.

If necessary, the patient may be sedated in order that the initial discomfort may be less. This will insure better cooperation if several injections should prove necessary, since the patient will agree more readily to repeated injections if the pain can be reduced. (Case 2, Fig. 3.)

It is thought by some clinicians that injection of the tubes offers a better hope of correcting obstruction than can be offered by surgical means (that is, by laparotomy and salpingotomy). A case, illustrating the use of this instrument for the purpose of opening the tubes, is shown. (Fig. 3.) This is a case which, on repeated occasions, had been found (by salpingography) to have an obstruction of the uterine end of the tubes. This is, of course, the type of obstruction in which surgery offers little hope. The type of tube obstruction which offers the greatest hope of correction surgically, is the obstruction which occurs at the distal end of the tube, thus permitting the removal of a portion of the tube and cuffing back the end of the tube with the hope of preventing a recurrence of the clubbing and its consequent obstruction. The case shown, after having failed to open when the old method was used, responded to therapy with the new cannula.

This instrument has been used in over 60 hysterosalpingographic studies, over a period of more than one year. The method has been found to be simpler and much more satisfactory than the one formerly employed.

One tuboovarian abscess resulted from the injection. This was, apparently, a poorly chosen case in which there flared up an unrecognized adnexal disease that had not adequately subsided. In this case, it is believed that any method of injection would have caused the same result. The modified technique was, therefore, not considered to be a factor.

### Conclusions

When employing the new technique (using new, self-retained, indwelling cannula-with-valve) for hysterosalpingography, the following points should be noted:

1. Simplification of technique.
2. One-plate method (instead of the two-or-more plates, 24-hour method).
3. Examination completed within one hour instead of 24 hours.
4. Less pain and trauma for patient.
5. Less expensive for patient.
6. More quickly and satisfactorily accomplished by physician.
7. Functional obstructions of Fallopian tubes (spasms, mucous plugs) fewer and more easily overcome because of more effective therapeutic action.
8. Films are clearer: fewer instrument shadows, thus more satisfactory interpretation.
9. Early medium spill, with instrument in place, gives better orientation.

10. An effective, satisfactory 30- to 60-minute plate makes available the lighter, more easily absorbable opaque medium base (peanut oil base).
11. Therapy: To open obstructed tubes.
  - A. More effective (because of prolonged, sustained, gentle, rhythmic pressure can be retained for 24 hours).
  - B. More easily accomplished.
  - C. More adaptable to repeated treatments (sedation may be used).
  - D. Less painful.
  - E. Uterine-tubular pressure found more effective than surgery (laparotomy, salpingotomy).
12. Film interpretation.
  - A. One plate is usually adequate.
  - B. Completely patent, freely movable tubes rarely shown fully outlined after 30-minute interval.

I wish to thank Dr. E. W. Squire, Charleston, W. Va., for his helpful suggestions and advice.

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## A NEW SELF-RETAINING VAGINAL RETRACTOR\*

### For Postpartum Cervical Inspection and Repair

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*(From the Obstetrical Department of the Cedars of Lebanon Hospital)*

**P**OSTPARTUM cervical inspection and repair are difficult unless the cervix can be well visualized. There has been great need for a cervical speculum which provides good exposure of the cervix and retains itself in the vagina so that it cannot be displaced by such movements as vomiting, or by manipulations such as traction on the cervix. Such an instrument should be simple in construction and easy to control.

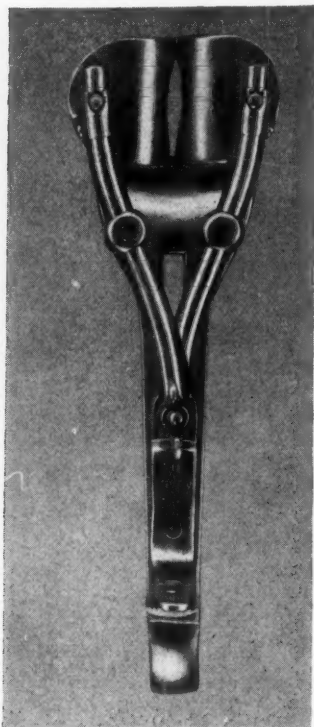


Fig. 1.—Retractor closed.

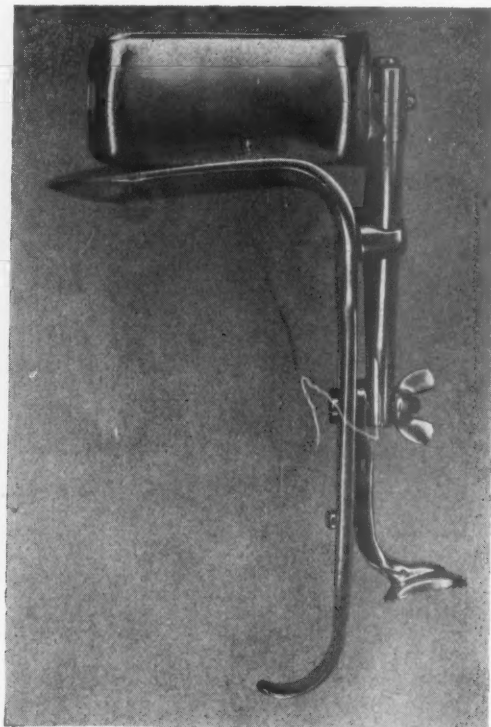


Fig. 2.—Retractor closed, seen from side.

During the past two years, the retractor here described has been used satisfactorily at the Cedars of Lebanon Hospital by approximately 20 obstetricians, on several hundred cases. It provides adequate visualization of the cervix and retention of the retractor without injuring the tissues. It may be opened to any desired width and retains itself securely.

\*The new retractor is manufactured by Woods Professional Supplies, manufacturers of surgical instruments, 8442 Otis Street, South Gate, Calif.

The retractor consists (Figs. 1-3) of a relatively broad base-plate on which are arranged two broad rotatable side-blades. The side-blades are mounted on two rods, by means of which they can be pushed upward and outward, gently unfolding the vaginal walls and adapting themselves to the individual shape and direction of the pubic bones of this patient. The greatest possible width can thus be reached in each individual case regardless of whether the pubic arch be wide or narrow.

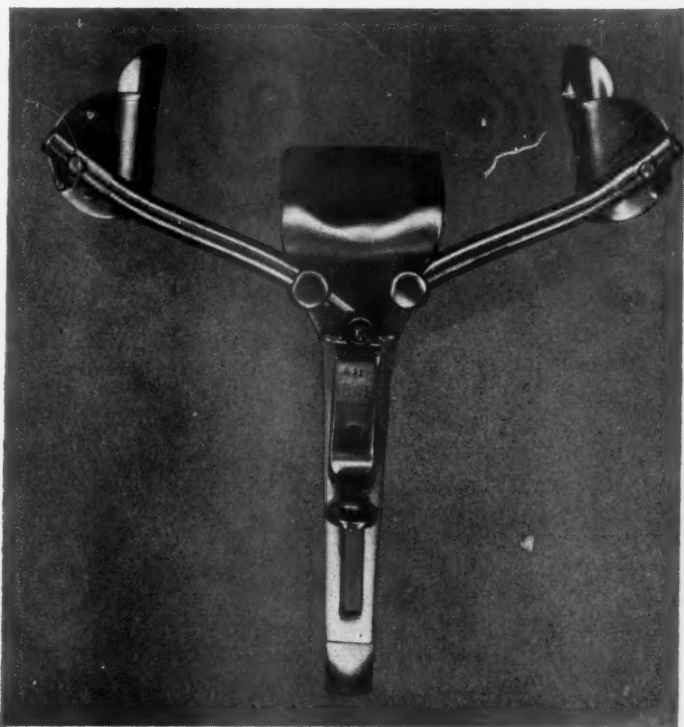


Fig. 3.—Retractor opened. Pressure of the thumb on the movable slide opens the retractor to the desired width. Tightening of the thumb-screw fixes the retractor in position.

The three-way movement of the blades provides an equal and symmetrical opening whereby the side-blades are brought in approximation with the pubic bones without exerting any pressure thereon. The side-blades are provided at their ends with hooks broad enough to anchor them firmly behind the pubic bones. The side-blades and base-plate open synchronously so that the retractor opens and retains itself at one movement. It needs no interchangeable side-blades of different length as it does not depend on the individual length of the vagina. Instead of attempting to hold itself by pressure against the soft mobile vaginal walls, it is held firmly behind the pubic bones.

This new obstetric self-retaining vaginal retractor should be especially helpful to obstetricians since the scarcity of interns and nurses makes operating without assistants the rule instead of the exception.

1322½ N. EDMONT STREET

## PLACENTA DELIVERED FIVE HOURS BEFORE BIRTH OF THE FETUS

RICHARD TORPIN, M.D., AUGUSTA, GA.

*(From the University Hospital)*

FOR a proper understanding of prolapse of the placenta (i.e., its delivery prior to the birth of the fetus), one should study the classic papers by J. Y. Simpson, Rucker, Bureczak, and Kobak and others, who have made more or less comprehensive analyses of the subject, besides reporting cases. J. Y. Simpson experimented with the idea of reducing maternal mortality in placenta previa centralis by manually removing the placenta in these cases before the delivery of the fetus.

Incidence of spontaneous prolapse of the placenta is extremely rare. In 8,000 supervised deliveries it has occurred only this once, and in 20,000 others delivered in this University Hospital over the past twenty-five years, my associates remember only one or two cases. Rare as it is, a well-trained obstetrician should have it in mind, and if it occurs when he is prepared for delivery, he may rapidly complete the second stage of labor with successful outcome for the fetus, as reported in two cases by Kobak and his associates.

In case the fetus is not viable or is dead, the treatment should be conservative for the sake of the mother unless there is maternal hemorrhage which probably is controllable by the onset of intensified labor contractions which force the presenting part into the cervical canal. A tight abdominal binder is of value also.

Other than in placenta previa centralis the most likely time for prolapse to occur is in the case of twins after the delivery of the first infant and before the birth of the second twin. In these cases manual delivery of the second twin by deep episiotomy and Kristellar expression or forceps, if presentation is cephalic, or by extraction if breech, or version and extraction if transverse, are the procedures of choice.

In all cases where a live infant is born, it may be in a state of partial to complete anoxia, and it is well to have at hand for immediate use an intratracheal catheter and an insufflator with a pressure control of 20 cm. of water (14 Hg.). If the fetus is markedly premature or already dead, and presents by head or breech, and there is slight vaginal hemorrhage, management by spontaneous delivery is safest for the mother from a standpoint of danger of infection and injury to the cervix. During the interval between delivery of the placenta and delivery of the fetus, the attendant should constantly observe the amount of vaginal hemorrhage and the progress of the presenting part which, when deeply engaged, successfully prevents further hemorrhage. In all cases, lost blood should be replaced immediately by transfusions.

### Case Report

M. L. D., Negro female, aged 26, weight 125 pounds, height 5 feet, 4 inches, small stature, had her last menstrual period February 2, 1944, and had felt life in June. On August 19, she began to bleed vaginally, more so at night than in the daytime and continued this to

August 25, when, at 3:00 P.M., she began to have uterine contractions and labor pains, which proceeded as in labor to 10:28 P.M., when she expelled the placenta without the membranes. The fetus remained in the uterus which contracted firmly around it.

Her blood pressure then was low, 60/40, due no doubt, to protracted blood loss, although there was only moderate hemorrhage at the time of delivery of the placenta or thereafter. She had entered the hospital with marked anemia, R.B.C. 2,670,000 and 8 Gm. hemoglobin, per 100 c.c., but because of her proving to be Rh negative, she had not received any blood transfusions.

However, because of her surgical shock condition following delivery of the placenta, she was given 1 pint of matched blood. Besides this, the treatment consisted of a tight abdominal binder and constant administration of oxygen by nasal tube. Approximately five hours later, at 3:10 A.M., August 26, she expelled the six months' stillborn female fetus which weighed 2 pounds, 2 ounces (963 Gm.), and was covered by the amnion. The fetus was not malformed, nor erythroblastotic. The placenta was circumvallate in process of formation. It measured 10 by 16 cm., and weighed 215 grams. The cord, 40 cm. long, was attached to the placenta eccentrically. The placenta had no gross appearance of erythroblastosis; it had one edge slightly darker in color on the fetal surface. There were no gross areas of infarction. The placenta probably was low lying, or even may have covered the internal os as in central placenta previa.

Lateral x-ray on August 23, revealed a six months' fetus in transverse presentation rather high in the uterus, with thin uterine wall shadow front, back and over the apex. From these facts, one can conclude that the placenta was entirely below the fetus at the time of making the x-ray film, two days before the onset of labor. She recovered without complications.

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## FETUS ADIPOCERE MONSTER

JOHN JOSEPH GILL, M.D., CHICAGO, ILL.

(From the Illinois Central Hospital)

**A**DIPOCERE is designated as a peculiar waxy substance formed during the decomposition of animal bodies, seen especially in human bodies buried in moist places. It consists principally of fatty acids and their salts called "grave-wax."

Mrs. F., aged 35 years, weighed 270 pounds. Her weight was 136 pounds ten years ago. Her menstrual periods began at the age of thirteen and were regular thirty-day type, lasting two days except during her pregnancies.

She has delivered four normal living children, each weighing eight to ten pounds at birth; the youngest is ten, the eldest sixteen years old; one spontaneous five-month abortion resulted from a fall four years ago.

Her last menstrual period occurred May 13, 1941, and considering herself in the menopause state, she did not consult her physician until the latter part of November.



Fig. 1.—Anterior view of fetus adipocere monster.

Dr. E. A. Wuesterman, without examining the patient, referred her to me for a diagnosis and treatment. I first saw her on December 15, 1941. Her ponderous abdomen, distended in every direction, was too firm to outline any contents within its boundary; vaginal examination gave only evidence of a thick, soft cervix. Three x-ray plates were taken before a faint shadow of an apparently abnormally developed, large fetus could be outlined.

The patient had not felt life at any time during this pregnancy, no fetal heart tones or movements could be elicited at this time. I decided for the present to keep her under observation and to await results.

On December 23, she developed painful contractions and entered the Illinois Central Hospital at 10:25 P.M. During her obstetric preparation

at 2:30 A.M., the membranes spontaneously ruptured and literally flooded the room, after which some hard, immobile, immovable, fetal body could be outlined within the uterus. The cervix was dilated to 3 cm. and the pains ceased. Quinine and castor oil did not assist labor.

After forty-eight hours from the beginning of labor pains, she developed a temperature of  $102^{\circ}$  F., blood pressure 90/60, red count was 3,610,000 and whites, 8,500.

December 26, after consultation with Drs. Charles M. Laury and Wm. T. Carlisle, a cesarean section was agreed upon and the following condition was found to exist: a mottled brown, statue-like figure of firm, almost brittle texture was adherent to the endometrium, which required blunt dissection to separate.

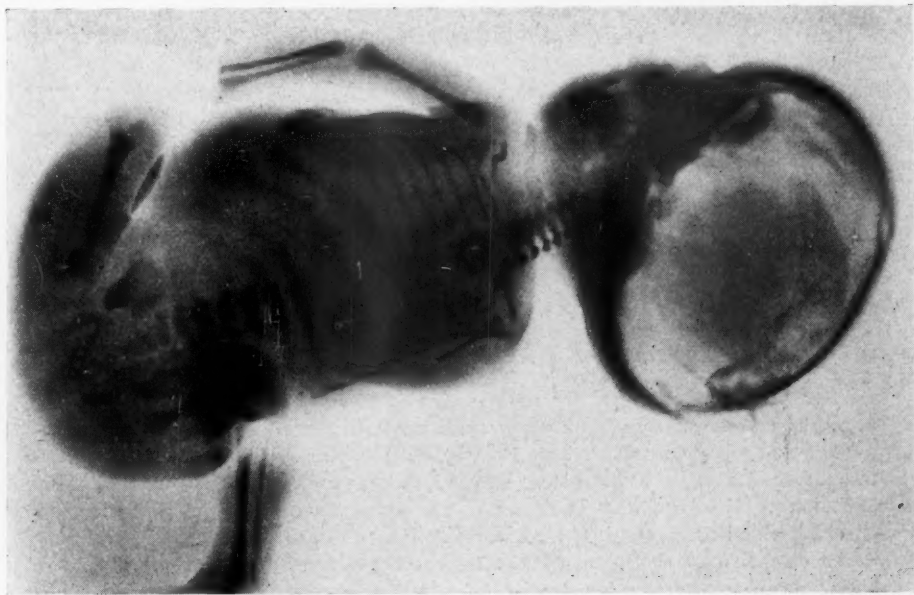


Fig. 2.—X-ray of fetus adipocere monster.

Upon attempting to remove the fetus, a hand snapped off at the wrist and likewise the right leg at the knee; there was no bleeding from these broken surfaces.

The female monster, resembling a wax doll, weighed eight pounds, measured 36 cm. from crown to rump, both feet and hands were clubbed, the cranium contained fluid and very little brain substance. The large placenta weighed one and three-quarters pounds.

The uterus with one tube and ovary was removed, followed by a stormy, septic fever for three weeks. The patient was discharged from the hospital on February 1, 1942, forty-two days after admission. She has remained in excellent condition at her last report of August, 1944.

The references consulted, mostly medicolegal and few in number, do not include any instances of fetal adipocere developing in utero.

# Department of Reviews and Abstracts

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## Selected Abstracts

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### Labor, Physiology, Management, Complications

**Radcliffe, Walter:** *The Blood Pressure in Labor*, Brit. M. J. 4340: 354, 1944.

The author is of the opinion that since barbiturates produce a hypotension, they should be used only in the early stages of labor, and they are best avoided within a short time preceding delivery. Hypotension during the third stage of labor is to be regarded as a danger sign, and the blood pressure should be restored before anything else is done. It is strongly urged that the sphygmomanometer be an important adjunct in the care of a woman during labor.

WILLIAM BERMAN.

**Norton, W. A.:** *Inversion of the Uterus*, Am. J. Surg. 63: 408, 1944.

After pointing out the rarity of inversion of the uterus, the author describes 2 cases. The first was seen some hours after its occurrence during delivery, attempts at reduction were unsuccessful, and the patient expired. In the second case, the inversion had also occurred during delivery, but was present for 6 months before admission to the hospital. The patient was markedly anemic and after repeated transfusion and other supportive measures had been utilized, a vaginal hysterectomy as the operation of choice was decided upon. In order to reduce hemorrhage to a minimum, the author used a tonsil snare over the wire of which a small rubber boot had been fashioned to grasp the inverted fundus almost to the level of the constricted cervix. When the rubber-protected snare was tightened, it acted both as a tourniquet and a tenaculum allowing the inverted fundus to be pulled well down so that it could be quickly removed with the electric cautery. The stump was sutured and pushed through the constricted cervix. The patient's convalescence was uneventful. The author recommends the use of the tonsil snare as described in similar cases.

FRANK SPIELMAN.

**Welton, T. S., and Ellingson, O.:** *Pregnancy and Delivery With an Intrauterine Pessary in the Cervix*, Am. J. Surg. 54: 484, 1941.

A case is reported of spontaneous delivery of a 2-pound, 6-ounce baby in a 37-year-old white gravida 8, who had worn a stem pessary continuously for 6 months prior to her pregnancy. Her membranes ruptured spontaneously 2 months before term, and at the time of admission, a moderate intrauterine infection was noted. The fetus was delivered easily and the stem pessary was found embedded in its scalp. It was removed without difficulty leaving a noticeable but transient impression of the appliance. Both mother and infant survived.

FRANK SPIELMAN.

**Robertson, H. E., and Dochat, George R.: Pregnancy and Gallstones, Internat. Abst. Surg. 78: 193, 1944.**

An extensive and complete historical review of the correlation between gallstones and pregnancy is herein presented. The commonly accepted statement that 90 per cent of women who have gallstones have borne children is traced to Naunyn's pupil, Heinrich Schroeder. The authors point out that these original figures are open to serious question because of an insufficient number of cases and are not suitable to the statistical conclusions derived from them.

It is further pointed out that to establish the predisposing effect of pregnancy on the production of cholelithiasis, it must be demonstrated that the percentage of gallstones in women with children is appreciably greater than the percentage of women who bear children in the population at large. When the figures of the present authors and their predecessors are analyzed on this basis, it is found that 79.25 per cent of all women have borne children. This figure corresponds very closely with the number of women with gallstones who have borne children. Therefore, while the percentage of women with cholelithiasis is 2 to 3 times that of men, there is no statistical evidence whatsoever that the phenomenon is related to childbearing.

L. M. HELLMAN.

### Newborn

**Bulfamonte, J. C.: Large Ovarian Cyst in Newborn Child, Am. J. Surg. 55: 175, 1942.**

This is a case report of a large ovarian cyst in a newborn infant recognized at birth, and soon after delineated by x-ray. Laparotomy was performed at the age of 5 weeks, and a neoplasm filling the entire abdomen and requiring aspiration was found. It arose on a long pedicle from the left ovary and was easily removed. A smaller cyst "about the size of an orange seed" was also removed from the right ovary. The pathologic report was cystadenoma.

FRANK SPIELMAN.

**Bakwin, Harry, and Patrick, Thomas W., Jr.: The Weight of Negro Infants, J. Pediat. 24: 405, 1944.**

The authors report a study of 114 Negro infants, making 679 observations from early life. On standard diets, these infants showed no significant difference in weight gain than white children during the first year of life, and that given proper medical supervision, Negro infants from moderate income families grow as well as white infants.

JAMES P. MARR.

**Hardwicke, Sarah Hooker: Studies on the Minimal Effective Dose of a Water-Soluble Vitamin K Substitute in the Prevention of Hypoprothrombinemia in the Newborn Infant, J. Pediat. 24: 259, 1944.**

A total of 87 breast-fed newborn babies were studied in an attempt to establish an approximate minimal effective daily dose of synkayvite (tetra sodium 2-methyl-1,4-naphthohydro-quinone diphosphoric acid ester).

They were divided into six groups, of which infants in five received doses of 0.5, 0.05, 0.005, 0.0005, 0.00005 mg. of the test substance daily, and infants in one of which served as controls. The substance was given orally.

The minimal dose of 0.0005 mg. given daily would probably prevent the development of hemorrhagic disease, except in a few cases. Approximately 1.25 mg. of the



test substance is apparently effective in lowering an excessively high prothrombin time to a normal range, i.e., 20 to 75 seconds; the danger zone lay between 70 and 100 seconds.

The administration of seconal, nembutal, and sodium amytal to mothers of the babies studied in this series had no demonstrable effect in prolonging the prothrombin time of the babies. Of interest was the baby born from a mother with a placenta previa, and an estimated hemorrhage of 500 c.c. of blood. This prothrombin time was 135 seconds. Mineral oil administered orally has been shown to lower the blood prothrombin of experimental animals.

JAMES P. MARR.

**Potter, Edith L.: A Double Ova Pregnancy in Which the Rh Positive Twin Developed Erythroblastosis, J. Pediat. 24: 449, 1944.**

An interesting case is reported of twins, one of whom died of erythroblastosis while the other remained normal. The affected twin and the father were Rh positive, the normal twin and the mother were Rh negative.

It is contended that the father was heterozygous for the Rh factor and that two ova were fertilized, one by a sperm carrying Rh-positive gene and the other a sperm carrying an Rh-negative gene. The Rh-negative mother had been sensitized to the Rh factor either in the previous pregnancy, when an Rh-positive fetus had been carried, or possibly during the course of this pregnancy by the Rh-positive twin.

The fetus whose cells were agglutinated developed erythroblastosis. The one whose cells were not agglutinated remained well.

JAMES P. MARR.

### Pregnancy, Complications

**Bottiroli, Ernesto: Diagnosis of Fetal Death by Determination of Coagulation Time of Maternal Blood, Bol. Soc. de obst. y ginec. 22: 464-470, 1943.**

The author states that coagulation time of normal gestating women varies between 12 minutes, 15 seconds and 15 minutes, 18 seconds. In 32 patients carrying dead fetuses in the last trimester of pregnancy, he found that the coagulation time was about 5 minutes. In 10 women with dead fetuses in the earlier stages of pregnancy, the coagulation time was at least twice as long. But in all cases seen 12 to 21 days before expected delivery, there was a striking reduction in coagulation time (10 to 13 minutes below the normal value). Hence, in doubtful cases of fetal death, determination of coagulation time is a useful procedure. Diagnosis is definite if the time is around 5 minutes. The method can be used only in the last three months of pregnancy.

J. P. GREENHILL.

**Duek, H.: Hemotherapy in Pernicious Vomiting, An. brasil. de ginec. 17: 197-203, 1944.**

The author treated 100 cases of pernicious vomiting of pregnancy by means of autohemotherapy. The patients were given daily injections of 10 c.c. of blood for three successive days. Satisfactory results were observed in 94 cases. The remaining six patients were relieved by auto-urine therapy. Symptoms other than vomiting were also relieved. There were recurrences of vomiting in 10 cases. A second course of autohemotherapy was given with success. Two patients had 3 courses of treatment.

J. P. GREENHILL.

**Zuckermann, C.: Uterine Myoma and Pregnancy, Rev. mex. de cir., ginec. y cáncer. 11: 307-312, 1943.**

The author describes a primipara, 28, in whom pregnancy occurred despite the presence of a large myoma between the cervix and body of the uterus. A living child that weighed 3 kg. was delivered by cesarean section, since the large tumor prevented a natural delivery. Suppurative and gangrenous metritis and an intra-peritoneal abscess developed, which, with the large tumor, necessitated subtotal hysterectomy. Appendectomy also was performed, since the appendix was adherent to the uterus. The patient recovered satisfactorily. The wound was closed with drainage after extirpation of all the lesions and local application of 6 Gm. of sulfathiazole intraperitoneally.

J. P. GREENHILL.

**Eckerson, E. B.: Primary Ovarian Pregnancy, Am. J. Surg. 54: 487, 1941.**

In 339 cases of ectopic pregnancy seen at the St. Luke's Hospital, New York City, during the past 40 years, there was only one case of primary ovarian pregnancy, an incidence of 0.2 per cent. The case is here presented. It occurred in a 38-year-old gravida i, para 0, whose previous pregnancy terminated in miscarriage 20 years before. There was no skipped period since her last menstruation had taken place 2 weeks before the onset of symptoms. The clinical picture was that of a ruptured Graafian follicle with intra-abdominal hemorrhage. At operation, the tube was uninvolved and the ovary was the site of what appeared to be a ruptured follicle bleeding actively. A salpingo-oophorectomy was performed. Pathologically, the tube was normal, and the ovary showed the ovarian pregnancy which satisfied the requirements as postulated by Spiegelberg and by Williams and Norris. No corpus luteum was found in either ovary.

FRANK SPIELMAN.

**Da Costa, L. A. Correa: Myomectomy and Pregnancy, An. brasil. de ginec. 16: 438-441, 1943.**

The author reports a case of myomectomy during the fifth month of pregnancy, followed by spontaneous delivery at term. The incidence of this association is variously given as from 0.03 to 0.7 per cent, but among 1,661 maternity cases the author observed 25 of myoma, or 1.5 per cent, possibly because 58.8 per cent of the patients were colored or mulattoes.

Of the 25 cases, 13 were diagnosed only during the puerperium, 6 during labor and 6 during pregnancy. Five were operated upon: one each for hemorrhage of the pedicle, pains and coexistence of ovarian cyst, obstruction of the pelvic canal and lack of space. The patient with obstruction of the pelvic canal had a Porro operation; the other interventions were simple myomectomies during pregnancy. There was no interruption of pregnancy or any serious complication during labor or the puerperium.

The author's opinion favors the view that present obstetric resources allow an expectant attitude toward these cases. Surgical intervention is imperative when complications arise, such as necrobiosis, torsion, hemorrhage, compression, uterine incarceration, etc., or when there is lack of space as with large myomas. In these cases, the operation should always be myomectomy when possible. Hysterectomy is reserved for infected cases, those in which myomectomy is technically impossible, or in which the uterine cavity or the membranes have been accidentally opened.

J. P. GREENHILL.

Noyola, J. N.: *Clinic of the Dead Fetus*, Rev. de cir. mex. 15: 417-424, 1943.

The author classifies the causes of death into maternal (general and local) fetal and ovular; in some cases the cause remains unknown. In 20 cases collected by him, the cause was syphilis in seven, intoxication of renal origin in four, typhoid pneumonia, malaria, placenta previa, decidual endometritis and thrombosis of the vessels of the umbilical cord in one each, and unknown in three.

If the fetus is expelled during the first hours after its death, it shows no changes; if weeks or months pass before expulsion, the changes range from dissolution to mummification and maceration of varying degrees. During any of these changes, the fetus may become infected, especially by anaerobes which produce putrefaction.

The symptoms vary with the period of pregnancy during which the fetus dies. Auscultation is of great value. When the fetus putrefies, symptoms of intoxication appear in the mother, and percussion reveals tympany of the uterus due to the gases of putrefaction which usually escape through the vulva. The laboratory may be of great help in making or confirming the diagnosis. Fetal death is immediately followed by a considerable decrease in the gonadotropic hormone of the blood and urine. Roentgenography furnishes important data, especially in the last months of pregnancy (overriding of the cranial bones and exaggerated flexion of the vertebral column).

During labor, the fetus may show signs of asphyxia, such as cardiac changes, altered fetal movements and evacuation of meconium, which indicate immediate intervention.

When death of the fetus is diagnosed, treatment must be individual, although some general rules can be established on the basis of the stage of the pregnancy and the changes in the fetus. During the first three months of pregnancy, spontaneous abortion occurs in the first few days following fetal death. If the fetus is retained, spontaneous evacuation is awaited, unless the membranes are ruptured (limited waiting), or the fetus becomes putrefied (immediate evacuation; total hysterectomy if the mother shows signs of grave infection).

When it has been impossible to determine the cause of the fetal death, it is advisable to treat the case with vitamin E in sufficient and prolonged dosage. The use of oxytocics should be limited and prescribed exclusively by physicians.

J. P. GREENHILL.

Delascio, D., and Rudge, W. de Souza: *Dystrophia-Dystocia Syndrome*, An. brasil. de ginec. 16: 415-427, 1943.

The authors report two cases and stress the necessity of a wide knowledge of this pathologic obstetric picture. The term of dystrophia-dystocia syndrome was used by Greenhill in an article published in *Surgical Clinics of North America* in 1924. He called attention to the relative sterility of these patients, and stated that frequently they conceived only once and late in life. Their external aspect is heavy with short extremities and masculine and hyperpituitary characteristics. The pelvis is narrow and there is a familial history of dystocia. Their pregnancies go beyond term, frequently present early rupture of the membranes with irregular contractions, and the position of the fetus is occipitoposterior. Greenhill described seven cases and recommended the low, cervical cesarean section for these patients.

According to DeLee, the syndrome is characterized by the following manifestations: 1. Pelvis of male type or slightly justo minor, with obesity localized to the trunk and roots of the extremities and simultaneously other signs of adipogenital dystrophy, small cervix and narrow rigid vagina. 2. Late primiparity. 3. Hypermaturity of the fetus (prolonged pregnancy). 4. Absence of engagement

of the fetal presentation when labor begins. 5. Occipitoposterior position. 6. Early or premature rupture of membranes. 7. Weak contractions with prolongation of the first stage of labor. 8. Familial dystocia. 9. Tendency to eclampsia. He points to the numerous mechanical difficulties which may arise in these cases during labor. He states that, owing to genital hypoplasia, frequent in these cases, delivery by the vaginal route is accompanied by extensive lacerations of the cervix and other soft parts and that uterine atonia often occurs. Finally, after delivery, he often felt that, if these difficulties could have been foreseen, cesarean section would have been the best course from the beginning.

It would seem that the syndrome is found once in 200 labors, or once in 80 labors of primiparas. It occurs in the various women of the same family, and the patient frequently is an only daughter. The diagnosis offers no difficulty for those who remember the typical clinical characters of the disease which have been stressed by all authors who have treated the subject. Unfortunately, the diagnosis is rarely made in daily practice, and this results in disastrous consequences for mother and fetus: for the former, lacerations, puerperal infection, psychoses, etc.; for the latter, high mortality and, in those who survive the traumatizing labor, the results of intracranial hemorrhages.

Considering the poor prognosis of vaginal delivery, the authors insist on cesarean section as the only therapeutic method.

J. P. GREENHILL.

**Vaccaro, H., and Meza, A.: Hemoagglutinin Rh and Fetal Erythroblastosis, First Investigations Made in Chile, *Rev. chilena de pediat.* 10: 717-733, 1943.**

The authors studied the Rh factor in 172 individuals and, after elimination of those connected with erythroblastosis, found 92.5 per cent of Rh positives and 7.5 per cent of Rh negatives. The percentages of Rh positives in the white race of the United States are 85.

The typical combination of Rh-negative mother and Rh-positive child could be established in all cases of erythroblastosis.

Iso-immunization and consequent incompatibility as a result of transfusions were demonstrated by post-transfusion shock and by fatal erythroblastosis in one case in a primipara, who had previously received transfusions of Rh-positive blood.

The authors propose the term of "created incompatibility" to differentiate the new concept from normal incompatibility. In materno-fetal iso-immunization, the incompatibility is created naturally, while the repeated transfusions confer an artificially created incompatibility.

The created incompatibility should be investigated in any post-transfusion shock, remembering that the red cells of the donor in the blood of the recipient may falsify the result of the reaction; it is advisable to repeat the test several days later.

In the treatment of the hemolytic diseases of the newly born infant, it is preferable to use Rh-negative blood because its red cells survive longer and have a better therapeutic effect, and it is imperative to discard blood sensitized to agglutinin Rh.

The authors are now studying the presence of maternal hemolysin and its curve during pregnancy because they think it possible to diagnose the Rh factor in the child during its intrauterine life.

Of 61 pregnancies studied, 35 ended with the birth of children having erythroblastosis, a percentage of 57.4 which offers considerable support to the new pathogenic concept of these diseases. There were 14 normal children: 3 were Rh negative and 11 Rh positive. With the exception of two, the latter were children of primiparas supporting the theory that iso-immunization is only started during



the first pregnancy, and has not yet produced a sufficient concentration of anti-Rh hemolysin to induce erythroblastosis. The same conclusion is reached by comparing the number of cases of erythroblastosis in primiparas and multiparas, 8.5 and 91.4, respectively.

In none of the 12 cases of abortion and of death in utero was it possible to demonstrate the intervention of the Rh factor. This favors the authors' thesis that iso-immunization and, with even more reason, the transplacental passage of the maternal agglutinin into the fetal circulation occurs mostly during the final stage of pregnancy and during labor.

On the basis of their experiences in various studies on placental permeability, the authors suggest a method to prevent hemolytic diseases in the newborn infants. In pregnancies with the probable prognosis of erythroblastosis, premature birth should be procured before the placental tissue reaches its maximal permeability, or, still more radically, cesarean section should be performed to avoid uterine contractions, and thus protect the child from the action of the anti-Rh hemoagglutinins of the maternal organism.

J. P. GREENHILL.

**Coatz, A. S.: Chronic Appendicitis and Pregnancy, *Semana méd.* 51: 370, 1944.**

In the opinion of Coatz, chronic appendicitis is an affliction which is frequently encountered in maternity services. The symptoms are identical with those in nonpregnant individuals. The diagnosis in pregnancy, however, is not always easy. The treatment during gestation should always be medical and should consist of proper diet, rest, applications of ice if necessary, and strict observation of the pregnancy. In the puerperium, an appendectomy should be performed in order to avoid a similar attack.

J. P. GREENHILL.

### Toxemia

**Sage, Earl C.: The Care of the Parturient Woman in Relation to Neonatal Mortality, *J. A. M. A.* 124: 339, 1944.**

The author discusses birth trauma, asphyxia, prematurity and maternal complications in relation to neonatal mortality. With regard to fetal asphyxia, prevention is as important as treatment. A proper anesthetic and a trained anesthetist are essential. Maintenance of body heat is also essential. Control of prematurity is also important in reducing neonatal mortality. Maintenance of body temperature, proper nutrition of the infant, prevention of cyanotic attacks, and prevention of infection are essential in this respect. Improved obstetrics is the best way of combating trauma. The numerous maternal complications affecting neonatal mortality are mentioned and discussed.

WILLIAM BERMAN.

**Dubrovsky, Ricardo, and Linzoain, Enrique A.: Treatment of Pulmonary Embolism Complicating Puerperal Thrombophlebitis, *Semana méd.* 51: 64-66, 1944.**

The authors state that pulmonary embolism results in exaggeration of vasoconstrictor, respiratory and cardiac reflexes and treatment is directed toward blocking these reflexes and dilating blood vessels. Morphine is used for the former, and papaverine in large doses intravenously for the latter.

Treatment is individualized according to the severity of signs and symptoms. In the presence of severe symptoms, 2 to 7 c.c. of a solution containing 0.03 Gm. of papaverine hydrochloride per cubic centimeter is injected slowly into the vein.

Simultaneously 0.01 to 0.015 Gm. of morphine hydrochloride is injected intramuscularly. In extreme instances, the morphine may be administered intravenously in a different vein from that being used for papaverine injection. In cases of lesser intensity, the papaverine is injected slowly and in the above dosage, but the least possible quantity of morphine (0.005 Gm.) is given, to avoid excessive depression of the respiratory center. In the mildest cases, 0.02 to 0.04 Gm. of papaverine is given intravenously without morphine. These dosages are rigidly followed, but varied according to individual indications. The highest dose of papaverine used by the authors was 0.20 Gm. on one occasion. Other authors have reported using even higher doses, but they have not found this necessary.

In most cases, even those with most severe symptoms, a favorable effect is produced by intravenous injection. As soon as vasodilatation occurs, the symptoms cease, the patient shows improvement and the injection can be stopped. Symptoms may recur with less intensity after several hours, when the injection is repeated. Even when symptoms do not recur, a second injection may be given as an adjuvant in the treatment of the pulmonary infarct which follows. A space of four hours has been arbitrarily set by some, but the authors believe the second dose should be administered according to the individual requirements of the patient.

Treatment of postembolic pulmonary infarct is similar to that for any acute pulmonary disease. Rest must be complete and prolonged and proper use of sulfonamides may prevent development of later sequelae. Inhalations of carbon dioxide are contraindicated unless too high dosage of morphine has depressed the respiratory center. Oxygen inhalations are valuable in treatment.

J. P. GREENHILL.

**Ferreira, Jorge, Cld.: Early Rising After Delivery and the Service of Obstetric Assistance in the Home, Rev. de ginec. e d'obst. 37: 288-291, 1943.**

The author states that the two are interdependent. Mother and child are sent home from the hospital between the third and seventh days and there they are attended and followed up by the service until complete recovery.

To be allowed up early, primiparas and multiparas must fulfill the following conditions: normal birth without traumatic or surgical lacerations, axillary temperature not over 36.8° C., normal lochia, firm uterine involution under 11 cm. from the pubic symphysis, normal urinary and digestive functions, regular milk function and good general condition. About 1 in 10 usually fulfill these conditions. Besides being beneficial, early rising increases the useful output of each maternity bed.

J. P. GREENHILL.

**Da Costa, Luiz Alfredo Corrêa: Revision of Uterine Cavity as Prophylaxis Against Puerperal Infection, Rev. de ginec. e d'obst. 37: 295-300, 1943.**

The author has used the method of Gheorghiu in 54 cases: 36 normal labors and deliveries except for retention of membranes, 5 normal labors followed by hemorrhage and manual extraction of placenta, 9 surgical births with retention of membranes and 4 surgical births with hemorrhage and manual extraction of placenta.

In the group of 36 cases, puerperal infection occurred in 2.7 per cent. Puerperal infection was listed when the temperature reached at least 38° C. twice in 24 hours.

In the other 18 cases, there were six infections; however, they occurred in severely ill cases: fever during labor in two, vaginal tamponing in two (one with perforation of uterus), forced dilatation with rupture of cervix in one and version after various trials of forceps in one.

There were no deaths, but the limited number of cases does not allow general conclusions.

The interesting cases are those of revision for simple retention of fragments of membrane, with an infection rate of 2.7 per cent which could even be reduced. In 100 similar cases under expectant observation sometimes helped by small doses of oxytocics, the incidence of puerperal infection was 8 per cent. Consequently, it is advantageous to revise the uterine cavity after birth when the membranes are not completely expelled, or when there is doubt about the integrity of the placenta.

Gheorghiu's method is as follows: The patient is anesthetized with ethyl chloride and, using all aseptic and antiseptic precautions the hand is introduced one or several times into the uterine cavity until it is completely cleaned of any remnants of membrane. Then the uterine cavity is washed with boiled water, using a Budin No. 30 sound and aiming only at a slight mechanical cleansing effect. The current of water must have low pressure and be stopped before the sound is removed, so that all water runs out first. The vagina is also washed out under low pressure. With this method, the morbidity rate in the author's clinic has fallen from 20 to 25 per cent in 1913, to 2 to 3 per cent at present.

J. P. GREENHILL.

### Vaginal Infections

Dubois, P.: **An Effective Treatment of Trichomonas Vaginalis Vaginitis**, Schweiz. med. Wchnschr. 74: 1944, 1944.

The trichomonas vaginalis belongs to the family of protozoal parasites in man and certain ones such as *Plasmodium malariae* and *Lambliia intestinalis* can be destroyed by quinine. By analogy, Dubois of the Lausanne Woman's Clinic reasoned trichomonas vaginitis should respond to quinine. He therefore experimented with many chemical agents and drugs, and found that in reality, quinine immobilized *Trichomonas vaginalis* more quickly than the other agents he employed. He therefore prepared vaginal suppositories containing quinine and used them in 25 women who had trichomonas vaginalis vaginitis. Only 10 women returned for regular treatments but the results were good. Relief was obtained after the use of two suppositories daily for 8 to 10 days.

J. P. GREENHILL.

Coutts, W. E., Brieva, J., Lerner, J., and Said R.: **Virus Infections of the Vulva, Vagina and Uterine Cervix**, Obst. y ginec. latino-am. 2: 9-21, 1944.

The authors examined a large series of prostitutes in Santiago, Chile, and found a number who had virus infection. A characteristic of such infections may be found in material obtained by biopsy. This consists of the presence of inclusion bodies found in the cytoplasm or nucleus, or in both, and their presence also in the intercellular spaces. Special staining methods have enabled the authors to study the chemical composition of these inclusion bodies and to make the correct diagnosis.

J. P. GREENHILL.

Rieper, J. P.: **Treatment of Trichomonas Vaginalis Vaginitis**, An. brasil. de ginec. 8: 257-267, 1943.

The author reports a series of 16 women treated for trichomonas vaginalis vaginitis by means of negatol. In this series 81 per cent were cured clinically but only 37.5 per cent were freed of the trichomonas organisms. Negatol produces a superficial necrosis which sterilizes the vagina, but reinfection takes

place because of secondary foci and primary sources of infection, and this is the main problem in the treatment.

J. P. GREENHILL.

**Dos Santos, A. F., and Zagury, S.: *Trichomonas Vaginalis* and Its Treatment, An. brasil. de ginec. 8: 167-178, 1943.**

The authors treat trichomonas vaginalis vaginitis by means of sulfonamide suppositories. Of 39 women treated by this means, 30 were cured and 9 discontinued the treatment. In 55.5 per cent of the cases, examination of the husband's urethra revealed the presence of *Trichomonas vaginalis*. This is the source of reinfection according to many authors. The organism was also found in the urethra of 33.3 per cent of the patients. No organisms were found in the rectum.

J. P. GREENHILL.

**O'Sullivan, J. V., and Bourne, L. B.: Supervision of Pregnant Women in Factory Employment, Brit. M. J. 4333: 108, 1944.**

The authors describe the British System of caring for pregnant women working in factories. Factory antenatal clinics are advised. Under medical supervision it was found that many women can do suitable work to an advanced stage of pregnancy. Nursing mothers were not advised to recommence work until at least three months after delivery, and day nurseries must be established if a return to work becomes necessary.

WILLIAM BERMAN.

**Dutra, Licinio H.: Sulfonamide Therapy in Gynecology and Obstetrics, Rev. de ginec. e d'obst. 37: 277-287, 1943.**

The author finds that the use of sulfonamides is obligatory in the prophylaxis and treatment of puerperal infection. Thus, any woman who had a prolonged delivery, premature rupture of the membranes, several vaginal examinations, assistance by nonprofessionals or an obstetrical intervention must be given sulfonamides. Whenever possible, their use should be started before the end of labor in doses of 4 to 5 Gm. daily, and after labor, oxytocics and blood transfusions should be administered, if necessary. The slight elimination of the drugs in the milk (2 to 6 centigrams in 24 hours) does not contraindicate breast feeding.

According to Speert, intravenous injection of sodium sulfathiazole or sodium sulfadiazine must be used in intercurrent or intrauterine infection during labor, or in cases of gonorrhea of the mother to protect the child.

Various sulfonamides have been successively used in the treatment of gonorrhea. Recent work by Douglas, Davis and Shandorf shows that sulfathiazole and sulfadiazine are more specific and rapid and much less toxic than sulfanilamide, and that sulfadiazine seems to be more efficient. Bacteriologic cure is frequently observed between 9 and 12 hours after the use of sulfadiazine and sulfathiazole, while sulfanilamide takes 40 to 50 hours to give the same result. The ideal form of treatment would consist of 4 Gm. of sulfadiazine or sulfathiazole daily for six consecutive days. These facts are being confirmed by the literature.

In gonococcal vulvovaginitis of infants the author has obtained much better results with estrogen therapy than with sulfanilamide or sulfathiazole.

The indications for the intraperitoneal use of sulfanilamide in powder are: peritonitis caused by bacteria or gastrointestinal contents; contamination of the sterile peritoneal cavity by opening of an infected cavity; a drained abscess cavity (Douglas); to avoid formation of adhesions in nonperitonized areas and in me-



chanical or chemical irritation; in exposure of the endometrium in the course of conservative myomectomy or hysterectomy; in cases of cesarean section performed in the presence of fever or old ruptured membranes.

Extraperitoneal indications for the use of sulfanilamide powder are abscessed or exuding cavities opened surgically (abscess of Bartholin's gland), incomplete and infected abortion without suppuration, impure forceps and version cases, vaginal and cervical laceration, uterine prolapse and other plastic operations of the lower genital tract and vaginal discharge due to trichomonas.

J. P. GREENHILL.

**Kirchoff, A. C., Racely, C. A., Wilson, W. M., and David, N. A.: An Ergonovine-Like Oxytocic Synthesized From Lysergic Acid, West. J. Surg. 52: 197, 1944.**

Addition of hydroxybutyl amide 2 to lysergic acid produces a compound that structurally resembles ergonovine, and produces a motor effect upon the uterus in every way similar to ergonovine. Tested on excised muscle strips of the guinea pig, rat, dog, and rabbit uterus it gave in comparable dosage, a motor reaction in every way comparable to ergonovine. Studies on the human being revealed an increased tone and motor response after a 3-minim dose by mouth in a woman near term. In 26 cases the drug was given in a dose of 0.2 mg. intravenously as the anterior shoulder was being delivered. The placenta was delivered in an average of 3.2 minutes and the reaction of the uterus in every way paralleled the response following comparable doses of ergonovine. There is a slight rise in blood pressure following the administration of M.E. 277 (Methergine), but apparently no sympathicolytic action because it failed to inhibit the epinephrine blood pressure rise in dogs and the epinephrine motor response in the rabbit uterus.

The synthetic preparation of such a product is important because of the limited ergot supply, and the difficulties found in obtaining potent raw material even where crude ergot is obtainable.

WILLIAM BICKERS.

**Leon, Juan: Obstetric and Obstetric-Gynecologic Specialization, Semana méd. 2: 667, 1943.**

The author comments on the controversy as to whether obstetric and gynecologic practice should be separated or combined. He points out that the essential function of the genital apparatus is reproduction. Gynecologic diseases are intimately concerned with the reproductive function; hence logically, study of physiology and pathology of the same organs cannot be separated. It is not necessary that a physician trained in obstetrics and gynecology should practice both specialties, but he will be better prepared to function as either type of specialist. In any case, however, specialization is indispensable.

A training program of six years is proposed. This is considered the minimum necessary to acquire in an orderly, disciplined form, the clinical experience necessary for practicing obstetrics. Specialization in obstetrics and gynecology simultaneously requires more time, at least ten years.

The suggested program comprises three cycles of two years each. The first period has for its object the general study of gynecology and everything pertaining to the physiology of pregnancy, parturition, the puerperium, and the newborn infant. The second period is devoted to the study of the pathology of pregnancy, parturition, the puerperium and the newborn infant. The third period covers the whole field of obstetrics. The candidate during the first two periods should serve as second assistant in the clinic, and in the consulting rooms, and should gain surgical experience as second assistant, first at simple operations and normal de-

liveries, and later in more complicated cases. During the third period, he should function as first assistant both in the clinic and the operating room, and should have first-hand experience in all types of pathologic and septic conditions.

J. P. GREENHILL.

**Brenner, F. T.: A New Breech Forceps, Am. J. Surg. 55: 181, 1942.**

A new type of forceps is described in which the handles meet the blades at an angle of almost 45 degrees. The blades are of the fenestrated Elliott type, and the handles fit together with a swivel action, being locked by a thumb set. The forceps are applied to the aftercoming head in breech deliveries over the shoulders instead of under, and extraction is accomplished by exerting pressure upward and over the mother's abdomen with a circular motion.

FRANK SPIELMAN.

**State, D., and Levine, M.: Human Plasma and Serum Toxicity, J. Lab. & Clin. Med. 28: 1786, 1943.**

That reactions occur in the course of serum transfusions has long been known. However, references to plasma reactions are meager so that it has been assumed that they do not take place. During the administration of several thousand plasma transfusions at the University of Minnesota Hospitals, the authors observed that reactions were not infrequent. In order to determine the factors involved in causation, they investigated the group specific plasmas by skin test especially with regard to the A and B substances. Sensitivity could be demonstrated to either, or to mixtures of A and B in individuals who developed reactions from their use. The conclusion reached was that plasma pooling is not a sure method of preventing reactions due to these substances. When the A and B factors are not involved, the following may also cause disturbances: 1. The presence of allergins in the plasma or serum. 2. The presence of reagins in the plasma or serum. 3. The presence of pyrogens. 4. The presence of immunologic factors as yet unknown. The authors conclude that skin test using the specific plasma to be transfused is a good method of indicating sensitivity in many cases and an aid in preventing transfusion reactions.

FRANK SPIELMAN.

## Items

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### American Board of Obstetrics and Gynecology

#### Examinations

The general oral and pathology examinations (Part II) for all candidates will be conducted at Atlantic City, New Jersey, by the entire Board from Thursday, June 14, through Tuesday, June 19, 1945. The Hotel Shelburne in Atlantic City will be the headquarters for the Board. Formal notice of the exact time of each candidate's examination will be sent him several weeks in advance of the examination dates. Hotel reservations may be made by writing direct to the Hotel.

Candidates for re-examination in Part II must make written application to the Secretary's Office not later than April 15, 1945.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

Deferment without time penalty under a waiver of our published regulations applying to civilian candidates, will be granted if a candidate in Service finds it impossible to proceed with the examinations of the Board.

Applications are now being received for the 1946 examinations. For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.

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## Necrology

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WILLIAM LATZKO, M.D., obstetrician and gynecologist, former professor at the University of Vienna and chief of the department at the Kaiserin Elizabeth Hospital in that city, died in New York after a prolonged illness, at the age of 81, on Feb. 11, 1945. A pioneer in the treatment of osteomalacia with phosphorus, a leader in the development of female urology as a part of gynecologic practice, universally known for the operation of extraperitoneal cesarean section named for him, the author of many contributions to the literature, he left Vienna in 1938 and practiced in Buenos Aires for several years before coming to this country where he remained active until his death.

